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Mecanismos neurales y conductuales de la inhibición de la conducta

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PRESENTADA POR

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y dirigida por: José Antonio Hinojosa Poveda, Jacobo Albert Bitaubé y Miguel Ángel Pozo García

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RESUMEN

La presente tesis doctoral examina los correlatos electrofisiológicos y conductuales de la inhibición selectiva, un tipo de inhibición de respuesta escasamente investigado. La selectividad del proceso inhibitorio es necesaria cuando los individuos deben lidiar con un entorno en el que están presentes múltiples estímulos, algunos de los cuales requieren interrumpir una respuesta (señales *stop*), mientras que otros requieren continuar respondiendo (señales *ignorar* o *continuar*). Previamente, la tarea de inhibición selectiva a nivel del estímulo se ha utilizado para explorar este asunto asumiendo que todos los participantes interrumpían su respuesta motora en curso de forma selectiva ante el estímulo *stop* pero no ante el estímulo *ignorar*. Sin embargo, los hallazgos recientes a nivel conductual sugieren que algunos individuos parecen interrumpir sus respuestas de forma no selectiva ante ambas señales. En la presente tesis doctoral, se detectó y controló por primera vez, según nuestro conocimiento, la estrategia cognitiva que adoptó cada participante al realizar una tarea de parada selectiva a nivel del estímulo antes de examinar los mecanismos neurales asociados con el proceso de cancelación de respuesta. En concreto, se examinaron los correlatos electrofisiológicos de la cancelación de respuesta en cada una de las estrategias para resolver un paradigma de inhibición selectiva a través del análisis de los potenciales evento-relacionados (PER) y de las dinámicas oscilatorias, tanto a nivel de cuero cabelludo como de vóxel. Los resultados apoyaron la clasificación conductual de las estrategias: se observaron efectos específicos dependiendo de la estrategia adoptada por los participantes. Así, cuando se compararon las condiciones *stop-acierto* (inhibición correcta de respuesta) e *ignorar* (ejecución de respuesta) para aislar la actividad neural relacionada con el proceso de cancelación, el incremento de activación ante la señal *stop* sólo fue evidente en aquellos participantes que habían empleado una estrategia en donde el proceso de interrupción de repuesta era selectivo ante las señales *stop* (la estrategia denominada *Discriminar y después Parar*). Este incremento de activación se observó al comienzo del componente P3 y en el rango de frecuencia beta-alto. El origen estimado de estos efectos se localizó principalmente en regiones prefrontales izquierdas, incluida el área motora presuplementaria, el giro frontal inferior y la corteza prefrontal dorsolateral (CPFDL). El comienzo de esta activación coincidió temporalmente con el momento de terminación del proceso de parada de la respuesta para esta estrategia (esto es, el tiempo medio estimado de inhibición). Por el contrario, en aquellos participantes que usaron la estrategia caracterizada por una parada de respuesta inespecífica, no se observaron diferencias de activación entre las condiciones *stop-acierto* e *ignorar* alrededor del tiempo estimado de inhibición. Con todo, estos resultados aportan datos relevantes en el objetivo de identificar los mecanismos neurales específicamente relacionados con el proceso de cancelación de respuesta y proporcionan evidencia a nivel neural de la existencia de distintas estrategias para resolver satisfactoriamente tareas de inhibición selectiva a nivel de estímulo. El comienzo de P3 y las oscilaciones en el rango de frecuencias beta-alto, así como sus sustratos neuroanatómicos, parecen jugar un papel relevante en la cancelación de una respuesta motora ya iniciada durante los paradigmas de inhibición selectiva. Es necesario que futuras investigaciones confirmen y extiendan los hallazgos encontrados.

ABSTRACT

The present doctoral dissertation examines the electrophysiological and behavioral correlates of selective stopping, a form of response inhibition that has scarcely been investigated. The selectivity of the inhibitory process is needed when individuals have to deal with an environment filled with multiple stimuli, some of which require the interruption of an already response (*stop* signals) and some of which require continue responding (*ignore* or *continue* signals). The stimulus-selective stop-signal task has been used to explore this issue assuming that all participants cancel their ongoing motor response selectively to stop but not to ignore signals. However, recent behavioural evidence suggests that some individuals seemed to suppress their motor responses non-selectively to both signals. In this dissertation, we detected and controlled for the first time the strategy adopted by participants when they performed a stimulus-selective stop-signal task before examining the neural mechanisms associated with the response cancellation process. Specifically, we explored the event-related potentials (ERPs) and oscillatory correlates of response cancellation underlying each strategy, both at the scalp- and source-levels. The results support the behavioral-based strategy classification: specific electrophysiological effects were observed depending on the strategy adopted by participants to achieve the demands placed by the selective stopping task. Thus, when contrasting the successful stop versus the ignore conditions to isolate the neural activity related to response cancellation, increased activation to stop signals was only evident for those participants who were classified as using a strategy in which the response interruption process was selective to stop signals (the so-called *Discriminate then Stop* strategy). This increased activity was observed in the onset of the P3 component and in the high-beta frequency range. The estimated neural sources for these effects were mainly located at several left-lateralized brain regions, including the pre-supplementary motor area, the inferior frontal gyrus and the dorsolateral prefrontal cortex. The onset of these activations matches the timing at which stopping process finished in this strategy (i.e., the stop signal-reaction time *SSRT*). By contrast, in those participants who used a strategy characterized by stopping non-selectively (*Stop then Discriminate* strategy), no activation differences between the successful stop and ignore conditions were observed around the *SSRT*. Overall, current results shed light on the pursued aim of isolating the neural mechanisms of response cancellation and provide neural support for the existence of different strategies for a successful performance in stimulus-selective stopping tasks. The onset of the P3 and oscillations in the high-beta frequency range, and their underlying cortical substrates, seem to play a critical role in cancelling an already initiated motor response during selective stopping paradigms. Future studies are needed to substantiate and extend present findings.

1 INTRODUCCIÓN

La presente tesis doctoral se ha llevado a cabo en la Unidad de Cartografía Cerebral del Instituto Pluridisciplinar de la Universidad Complutense de Madrid dentro del grupo de investigación AFNECO ("Affective Neurolinguistics and Cognition Group"; https://www.ucace.com/bml/afneco/). Para el desarrollo de esta se ha contado con ayuda pública (Comunidad de Madrid y Ministerio de Economía y Competitividad) a través de los proyectos S2015/HUM-3327 y PSI2017-84922-R. En ningún caso, los organismos que han otorgado estas ayudas han influido en la presente investigación, ni en la planificación de la tesis, ni en la recogida de datos, ni en la interpretación de los resultados obtenidos.

1.1 Definición e implicaciones clínicas de la inhibición

El concepto de inhibición ha sido abordado desde numerosos ámbitos de estudio, como los de la filosofía, la psiquiatría, la psicología o la neurofisiología. La primera definición "científica" de la inhibición puede remontarse al campo psicología moral de Platón y Aristóteles, siendo inicialmente entendida como el mecanismo mediante el cual el intelecto controla las pasiones y la voluntad domina los impulsos (Smith, 1992). Por su parte, el uso del término inhibición en el ámbito de la fisiología no aparecería en absoluto ligado a las ideas de la consciencia y la voluntad, sino que fue más bien delineado, en oposición a la excitación, como uno de los sustratos más simples de la función nerviosa (Wundt, 1904).

Dada la existencia de distintas tradiciones, resulta imprescindible clarificar en primera instancia que el ámbito de estudio desde el que se abordará su análisis en el presente trabajo corresponde al dominio de la psicología y la neurociencia cognitiva. En este contexto, los primeros esfuerzos por profundizar en su caracterización tomaron como punto de partida las observaciones del funcionamiento de la estimulación nerviosa y los reflejos más simples y, desde aquí, se buscó tender puentes hacia otros fenómenos más propios de la conducta observable. Estas primeras aproximaciones permitieron definir conceptos tan importantes como la inhibición latente en el ámbito del condicionamiento clásico (Lubow y Moore, 1959) o como la inhibición de retorno en el estudio de la atención (Posner y Cohen, 1984).

Sin embargo, estas formas de inhibición tan próximas a la naturaleza del funcionamiento del propio sistema nervioso cubrirían solo los aspectos más automáticos de la inhibición, mientras que este constructo también abarcaría otros dominios relativos a comportamientos más sujetos al control voluntario de los individuos. Bajo este enfoque, la inhibición podría entenderse como un subcomponente del sistema ejecutivo, es decir, un conjunto de procesos cognitivos de orden superior encargados de supervisar y regular el funcionamiento de otros procesos de orden inferior en aquellos momentos en los que el comportamiento automático (aprendido) podría ser incompatible o insuficiente de acuerdo con la consecución de una meta (Miller y Cohen, 2001). Dentro de este sistema de funciones ejecutivas, la atención y la inhibición constituirían los elementos centrales y operarían bajo la asistencia de otros procesos auxiliares como la selección de planes de actuación, la actualización de los mismos y de las instrucciones en la memoria de trabajo, el cambio atencional y de comportamiento y la supervisión del propio desempeño (Figura 1).

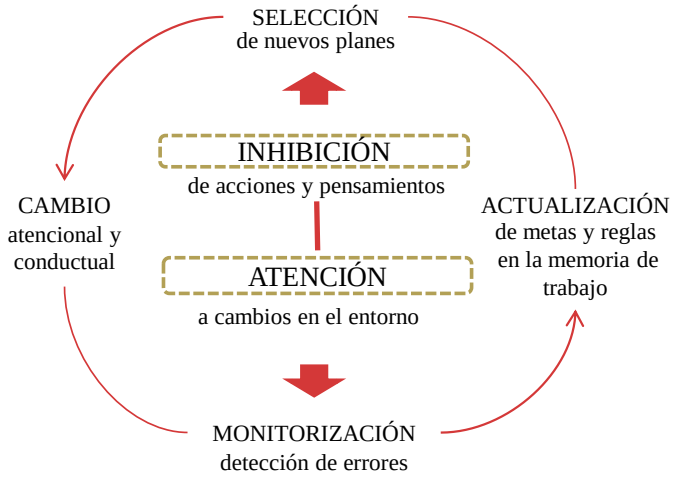

Figura 1. Representación esquemática de las diferentes funciones ejecutivas y su relación de forma simplificada. Adaptada de Bari y Robbins (2013).

Así, la inhibición, entendida como uno de los procesos nucleares del funcionamiento ejecutivo, implicaría la capacidad para regular la propia atención, los pensamientos y/o las emociones con el fin de suprimir ciertas predisposiciones internas o atracciones externas y en su lugar, hacer aquello que es más apropiado o necesario de acuerdo a la consecución de ciertas metas (Diamond, 2013).

Las alteraciones en el control inhibitorio representan una característica central de diferentes trastornos neurológicos, psicológicos y psiquiátricos. Atendiendo a la naturaleza de estas alteraciones y siguiendo la taxonomía propuesta por Jahanshahi, Obeso, Rothwell y Obeso (2015), estas dificultades podrían quedar agrupadas en términos de su excesiva o deficitaria presencia. Por un lado, la alteración conductual que con mayor claridad refleja la ausencia de la capacidad para controlar la propia conducta sería la impulsividad. Bajo esta etiqueta general se han clasificado dificultades tales como la inhabilidad para interrumpir una respuesta o un pensamiento, la preferencia por recompensas inmediatas, pero de menor valor sobre otras recompensas demoradas, pero de mayor valor, la actuación carente de reflexividad previa a disponer de toda la información necesaria, o la búsqueda de la novedad y las sensaciones y la propensión a implicarse en conductas arriesgadas (Bari y Robbins, 2013). Los rasgos de impulsividad son característicos de algunos trastornos clínicos como el trastorno por déficit de atención con hiperactividad (López-Martín, Albert, Fernández-Jaén y Carretié, 2015), el abuso de sustancias (Fillmore y Rush, 2002; Monterosso, Aron, Cordova, Xu y London, 2005), la esquizofrenia (Enticott, Ogloff y Bradshaw, 2008), el trastorno obsesivo compulsivo (Chamberlain, Blackwell, Fineberg, Robbins y Sahakian, 2005) o el trastorno límite de la personalidad (Albert et al., 2019). Adicionalmente, también podría considerarse que las perseveraciones (esto es, la repetición de respuestas que han dejado de ser apropiadas al contexto), se asocian con un deficiente control inhibitorio. En este sentido, tanto las conductas desinhibidas como las impulsivas o perseverativas son también características de pacientes con lesiones frontales adquiridas (Bechara, Tranel y Damasio, 2000).

Por otro lado, la acinesia es uno de los síntomas más comunes que presentan los pacientes con síndrome de Parkinson. Así, estos pacientes con frecuencia experimentan un bloqueo motor temporal durante la marcha que podría representar un ejemplo de excesiva inhibición. Asimismo, en el plano más emocional, este tipo de pacientes se muestran con frecuencia faltos de reactividad emocional, interés, motivación e iniciativa, lo que plantean la posibilidad de que la apatía y la abulia puedan relacionarse con una excesiva inhibición. Puede subrayarse, además, que la abulia o inhabilidad para tomar decisiones a menudo emerge como uno de los síntomas más característicos de las lesiones sobrevenidas de los ganglios basales en los seres humanos, una región cerebral que, como se verá posteriormente, juega un papel clave en la inhibición de respuestas junto con otras estructuras corticales.

De este modo, la identificación de los marcadores neurocognitivos relacionados con la inhibición y la impulsividad se erigiría como un objetivo clave para alcanzar una mejor comprensión de los factores de riesgo, la etiología y los tratamientos de un importante conjunto de trastornos neurológicos, psicológicos y psiquiátricos caracterizados por una alteración en los procesos de control inhibitorio (Aron, 2011).

1.2 Paradigmas experimentales para examinar la inhibición

Estudiar de forma experimental la inhibición en el contexto controlado de un laboratorio implica superar el reto de analizar una conducta que, por definición, no es observable. Por ello, abordar este desafío requiere una profunda comprensión del sistema de respuesta implicado en el contexto de la tarea. En este sentido, puede señalarse que bajo el paraguas general del concepto de inhibición expuesto hasta el momento encajaría tanto la interrupción de respuestas a nivel cognitivo y emocional, como la interrupción de respuestas motoras. De este modo, aunque existen paradigmas experimentales diseñados para estudiar la inhibición en ambos niveles, gran parte de la investigación sobre la inhibición se ha centrado en la interrupción de respuestas motoras. Esto ha sido debido al hecho de que la conducta objeto de estudio puede definirse con mayor facilidad al tratarse de una dimensión observable. Por ello, existe actualmente una amplia variedad de tareas de laboratorio para evaluar la inhibición de respuestas.

Este tipo de paradigmas tienen en común el hecho de inducir en los participantes una tendencia dominante de respuesta ante un estímulo específico (estímulo típicamente denominado *go*[1]), que deberá ser suprimida ante la aparición inesperada e infrecuente de un segundo estímulo (estímulo comúnmente denominado *no-go* o *stop*). De entre estos paradigmas, los más clásicamente empleados son la tarea *go/no-go* y *la tarea stop-signal* (Figura 2). Ambas tareas se asemejan en la aparición de un estímulo que marca la necesidad de emitir una rápida respuesta motora, pero difieren en la naturaleza del estímulo o señal que marca la inhibición de esta respuesta. Mientras que en la tarea *go/no-go*, los participantes pueden asociar la

[1] Se utilizarán los términos en inglés go (ir), no-go (no-ir), stop (parada) y tarea stop-signal (tarea de señal de parada) en lugar de su traducción en castellano dada su amplia utilización en este ámbito de conocimiento y con el fin de facilitar la lectura global de la tesis, la cual incluye artículos publicados en inglés. Asimismo, se emplearán las abreviaturas en inglés de los términos típicamente empleados en la investigación sobre la inhibición de respuesta.

conducta de inhibición con un estímulo de forma específica (ensayo *no-go*), en la tarea *stop-signal* es un estímulo *stop* presentado tras el estímulo *go* después de una demora variable el que señala la necesidad de inhibir la respuesta. Ese factor diferencial introduce un importante matiz a la hora de considerar qué tipo de inhibición de respuesta se estaría examinando con ambos paradigmas. Mientras que en la tarea *go/no-go* tendría lugar la contención de una respuesta dominante, en la tarea *stop-signal* se requeriría cancelar o interrumpir una respuesta previamente desencadenada por el estímulo *go*.

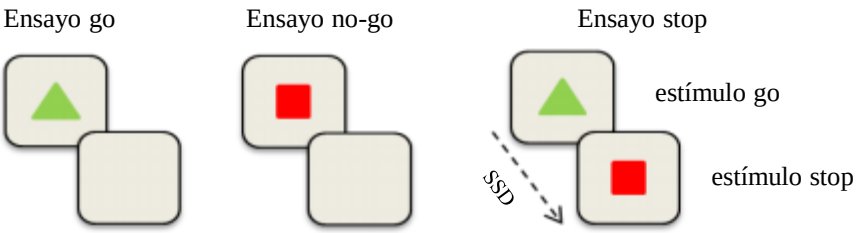

Figura 2. Tipos de ensayos en las tareas *go/no-go y stop-signal*. SSD: Stop signal delay (demora de aparición del estímulo *stop*).

Las variables dependientes a nivel conductual obtenidas en estas dos tareas de inhibición son la velocidad media de respuesta ante los estímulos *go* y la tasa de falsas alarmas (también denominados fallos inhibitorios o errores de comisión) ante el estímulo *no-go* o *stop*. A partir de los resultados derivados de la tarea *stop-signal* se ha desarrollado un modelo cognitivo que proporciona un contexto idóneo para el estudio de las bases cerebrales de la cancelación de respuestas motoras. Este modelo se fundamenta en dos evidencias comúnmente observadas en los estudios que emplean esta tarea experimental. En primer lugar, los datos señalan que la habilidad para cancelar una respuesta previamente iniciada es en realidad probabilística (Schall, Palmeri y Logan, 2017), ya que depende directamente del tiempo que separa los estímulos *go* y *stop* (esto es, de la demora con la que la señal *stop* aparece tras la aparición del estímulo *go*, lo que se ha denominado en inglés como *stop-signal delay o* abreviadamente *SSD)*. De esta forma, se ha observado de manera consistente que cuanto menor es el tiempo que separa los estímulos *go* y *stop* (esto es, se observa un *SSD* más corto), más probable es que el participante detecte a tiempo el estímulo *stop* y que logre cancelar su respuesta con éxito. Por el contrario, conforme mayor es la demora entre estos dos estímulos (esto es, se observa un SSD más largo), más probable es que acontezca un fallo inhibitorio. Adicionalmente, la segunda variable clave en la tarea *stop-signal* es la latencia del fallo inhibitorio (la emisión de una respuesta en un ensayo *stop*). Uno de los hallazgos clásicos obtenidos con esta tarea es que el tiempo de reacción (TR) medio en los ensayos en los que se ha cometido un fallo inhibitorio es menor que el de los ensayos *go* que requieren la emisión de una respuesta motora. Esto ha llevado a considerar que los tiempos observados en los fallos inhibitorios provendrían de la cola más rápida de la distribución de los TRs del participante ante los ensayos *go*.

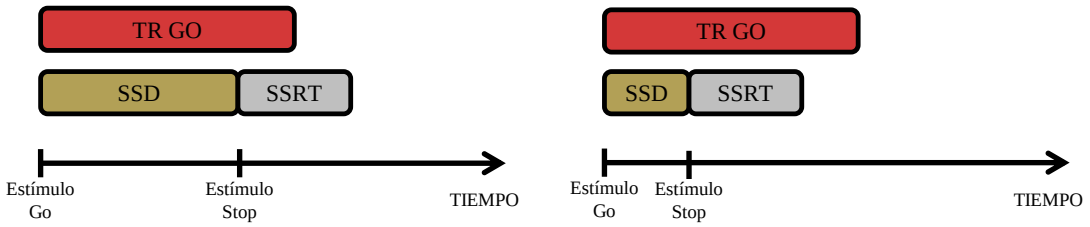

Figura 3. Modelo de carrera de caballos (Logan y Cowan, 1984). En el primer caso, el proceso *go* finalizaría antes que la suma del *SSD+SSRT* y por tanto la respuesta sería emitida, mientras que, en el segundo caso, la respuesta sería correctamente inhibida ya que la suma del *SSD+SSRT* es menor que el tiempo de reacción ante el *estímulo go*. *SSD*: stop signal delay (demora de la señal stop), *SSRT*: stop signal reaction time (tiempo medio de inhibición).

Estos dos efectos conductuales sugieren que la inhibición depende del resultado de una carrera entre un proceso de respuesta desencadenado por el estímulo *go* y un proceso de inhibición, iniciado por el estímulo *stop*. En caso de que el proceso de inhibición llegue a término antes que el proceso de respuesta, la respuesta sería inhibida con éxito. Sin embargo, si es el proceso de respuesta el que finaliza primero, la respuesta sería eventualmente expresada, produciendo un fallo inhibitorio (Figura 3). Esta propuesta quedó formalizada en el denominado *modelo independiente de carrera de caballos* (Logan y Cowan, 1984) en el que se representa el momento de finalización de ambos procesos como variables aleatorias independientes. Un aspecto relevante de este modelo es que permite estimar la latencia del proceso inhibitorio, pese a no ser directamente observable. Esta estimación recibe el nombre de tiempo medio de inhibición (*stop-signal reaction time*, *SSRT*). Brevemente, el cálculo de esta variable clave consiste en integrar la distribución de tiempos de reacción para estímulos *go* hasta que ésta iguale la probabilidad de fallar considerando una demora concreta entre el estímulo *go* y la señal *stop*. De esta forma, se identifica la latencia límite a partir de la cual comenzarían a producirse fallos inhibitorios dada esa demora. Por tanto, al descontar de esta medida la propia duración de dicha demora, se obtendría la latencia del proceso iniciado con la aparición del estímulo stop o tiempo medio de inhibición (*SSRT*) (Figura 4).

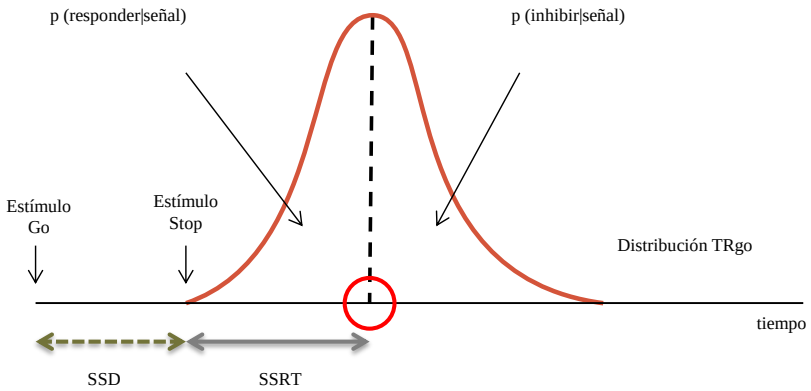

Figura 4. Representación gráfica de los supuestos del modelo independiente de carrera de caballos de Logan y Cowan (1984), indicando la probabilidad de emitir e inhibir una respuesta en un ensayo de inhibición dependiendo de la distribución de tiempos de reacción ante el estímulo go, la demora entre los estímulos go y stop (SSD) y del tiempo medio de inhibición (*SSRT*).

La estimación del tiempo medio de inhibición (*SSRT*) se ha llevado a cabo principalmente a través de dos métodos (Verbruggen y Logan, 2009). Mientras que de forma clásica el experimentador seleccionaba a priori varias demoras para estudiar la capacidad inhibitoria del participante, recientemente se ha implementado un procedimiento de ajuste adaptativo de esta variable en función del propio desempeño del mismo. Así, cada vez que en la tarea aparece un ensayo *stop*, la demora entre estímulos aumenta o desciende en un tiempo determinado (comúnmente, 50 milisegundos) en función de si el participante ha respondido correcta o incorrectamente, respectivamente. Tras unos pocos ensayos, este procedimiento permite determinar la demora con la que el participante es capaz de detener con éxito su respuesta motora aproximadamente en el 50% de los ensayos *stop*. Una vez satisfecha esta condición, la propia media de la distribución de tiempos de reacción *go* marca el final de la latencia del proceso de inhibición, simplificando considerablemente los cálculos que implica su estimación. Sin embargo, recientemente se ha demostrado que este método introduce sesgos sobre la estimación del tiempo medio de inhibición (*SSRT*) cuando la distribución de tiempos de reacción *go* no es normal, algo que ocurre con relativa frecuencia en la población general y, especialmente, en poblaciones clínicas (en estos, casos las distribuciones suelen adoptar formas asimétricas positivas; Verbruggen, Chambers y Logan, 2013).

La validez del *modelo independiente de carrera de caballos* ha sido ampliamente contrastada (Band, Van der Molen y Logan, 2003; Colonius, Özyurt y Arndt, 2001). No obstante, dado que este modelo está formulado en términos de las distribuciones del tiempo de finalización de los procesos de respuesta e inhibición, distintos autores han intentado profundizar posteriormente en la caracterización de los procesos computacionales y neurales subyacentes que serían los responsables de generar dichos tiempos de finalización (Boucher, Palmeri, Logan y Schall, 2007; Schall et al., 2017). Así, los datos obtenidos con paradigmas experimentales en los que se ha explorado la inhibición de los movimientos sacádicos han puesto de manifiesto que los procesos neurofisiológicos responsables de la inhibición de estas respuestas motoras serían, en realidad, altamente dependientes entre sí (Boucher et al., 2007). Estos hallazgos plantearon el reto de desarrollar un modelo de carrera independiente capaz de explicar de forma satisfactoria el comportamiento de sistemas de neuronas altamente interactivas. Con el objeto de solucionar este problema se planteó la existencia de una carrera de carácter interactivo entre los procesos de respuesta (*go*) e inhibición (*stop*), en la que las unidades correspondientes a ambos procesos permanecerían independientes durante la mayor parte de su duración, ejerciendo la unidad *stop* un breve pero potente efecto de interacción sobre la unidad *go* para interrumpir su respuesta al final de dicha interacción. Así, esta propuesta plantea que la mayor parte del tiempo medio de inhibición (*SSRT*) estaría ocupado por un periodo dedicado a codificar la señal *stop* (ya sea auditiva o visual), mientras que la interrupción de la respuesta podría considerarse prácticamente instantánea. Por ello, las estimaciones del tiempo medio de inhibición realizadas mediante el modelo de carrera independiente continuarían aportando una medida válida de los procesos de interrupción de respuestas motoras.

Como se mencionará más adelante, la presente tesis doctoral se centrará en la etapa última del tiempo estimado de inhibición (*SSRT*) que se relaciona específicamente con la cancelación o interrupción de una respuesta motora ya iniciada (Boucher et al., 2007; Schall et al., 2017). Para ello, se utilizará una modificación de un paradigma experimental (la tarea *stop-signal*) que permite estimar la latencia de este proceso inobservable a través un modelo conductual (*el modelo independiente de carreras de caballos*) ampliamente contrastado, tanto en humanos como en animales (Kornylo, Dill, Saenz y Krauzlis, 2003; Eagle y Robbins, 2003).

1.3 Bases neurales de la inhibición

Como elemento integrante de las funciones ejecutivas, el control inhibitorio implica un patrón de activación jerárquica controlado principalmente por estructuras prefrontales del cerebro que regularían el funcionamiento de otras estructuras de menor nivel (Norman y Shallice, 1986). A nivel cortical, datos procedentes de estudios con pacientes lesionados y de estudios con resonancia magnética funcional (RMf) han mostrado que el área motora pre-suplementaria y el giro frontal inferior derecho son las dos regiones más consistentemente relacionadas con la inhibición de respuestas motoras, (Aron, Robbins y Poldrack, 2014; Li, Huang, Constable y Sinha., 2006; Floden y Stuss, 2006). El giro frontal inferior comprende regiones de la corteza prefrontal lateral anteriores al surco precentral e inferiores al surco frontal inferior (Aron, 2011). Entre las regiones más características de esta estructura se encuentran el pars triangularis, el pars opercularis y algunas regiones del pars orbitalis (áreas de Brodmann, 44, 45 y 47). De todas estas regiones, el pars opercularis parece representar la región clave para la inhibición, ya que una lesión permanente en esta zona o una inhabilitación temporal de su función a través de la estimulación magnética transcraneal genera un importante deterioro en el control inhibitorio (Aron, Fletcher, Bullmore, Sahakian y Robbins, 2003; Chambers et al., 2006). Además, los datos obtenidos a partir de estudios de imagen por tensor de difusión señalan que el pars opercularis muestra un mayor grado de conectividad con otra de las regiones corticales más relevantes para la inhibición: la corteza motora pre-suplementaria (Aron, Behrens, Smith, Frank y Poldrack, 2007). Pese a que la lateralización de la actividad del giro frontal sugiere una mayor participación del hemisferio derecho (Aron et al., 2014), existe también evidencia de una activación bilateral de esta región (Cai y Leung, 2009; Li et al., 2006; Swick, Ashley y Turken, 2008). Por último, cabe señalar que existe cierto debate acerca de la especificidad de esta región en relación a la inhibición de respuesta, ya que parece que diferentes sectores de la corteza frontal inferior derecha podrían estar implicadas en otras funciones cognitivas más ligadas con la atención.

Por su parte, la corteza motora pre-suplementaria está localizada en la corteza frontal dorsomedial y, en concreto, en la pared medial del giro frontal superior (dorsal al cíngulo anterior y anterior al área motora suplementaria). Estudios previos han revelado déficits en el control inhibitorio tras la inactivación temporal de esta región o tras lesiones localizadas en regiones prefrontales solapadas con esta región (Chen, Muggleton, Tzeng, Hung, y Juan, 2009; Floden y Stuss, 2006; Nachev, Wydell, O'neill, Husain, y Kennard,

2007). Además, los resultados del estudio de Li y colaboradores (2006), en el que se empeló un diseño experimental que permitía aislar el proceso específico de inhibición de otros procesos perceptivos, cognitivos y afectivos que también se activan durante la realización de las tareas de inhibición, señalan también a la corteza motora pre-suplementaria como la principal estructura implicada en la inhibición de una respuesta motora. Pese a los intentos por destacar el papel de una de estas regiones sobre la otra en la inhibición de respuesta, la multitud de procesos diferentes involucrados en la misma permite plantear como más plausible la hipótesis de que sea más bien la interacción entre estas dos regiones la que permita la correcta interrupción de una respuesta motora (Bari y Robbins, 2013). De hecho, como se señaló anteriormente, se ha de mostrado que ambas regiones están fuertemente conectadas (Aron et al., 2007; Swan et al., 2012), aunque no existe evidencia concluyente sobre cuál de estas dos áreas se activaría en primer lugar (para una revisión, véase Arón et al., 2014).

Se ha observado la activación de otras áreas de la corteza en las tareas de inhibición de respuesta. No obstante, su implicación parece relacionarse más bien con otros procesos cognitivos necesarios para llevar a cabo la inhibición motora. Entre estas regiones cabría destacar a la corteza motora suplementaria, posiblemente relacionada con la propia selección de la respuesta (Mostofsky y Simmonds, 2008); la corteza parietal, implicada quizá como consecuencia de las demandas de atención viso-espacial intrínsecas de este tipo de tareas (Rubia et al., 2001); la CPFDL, probablemente asociada al mantenimiento de las instrucciones de la tarea (Levy y Goldman-Rakic, 2000); la ínsula, cuya activación podría ser inducida ante la necesidad de resolver la interferencia entre respuestas competitivas (Wager et al., 2005); o el córtex cingulado anterior, asociado también a la monitorización del conflicto (Botvinick, Braver, Barch, Carter y Cohen, 2001) o a la propia detección de errores (Kiehl, Liddle y Hopfinger, 2000). Esta disparidad de resultados muestra claramente la necesidad de incluir rigurosos controles experimentales que permitan interpretar con mayor fidelidad la especificidad de los resultados obtenidos a la hora de identificar las bases neurales asociadas con la inhibición y, más concretamente, con el proceso específico de cancelación o interrupción de una respuesta motora ya iniciada.

Aparte de las regiones cerebrales ya mencionadas, se ha descrito la participación de estructuras subcorticales en la inhibición de respuestas motoras. Tanto el giro frontal inferior como la corteza motora pre-suplementaria presentan importantes conexiones con los ganglios basales. Estos núcleos subcorticales estarían formados por el estriado (que aglutina tanto al núcleo caudado como al putamen), el globo pálido (divisible en sus segmentos interno y externo), la sustancia negra (que incluiría la parte reticulada y la parte compacta) y el núcleo subtalámico. Este conjunto de núcleos, además de relacionarse estrechamente con el giro frontal inferior y la corteza motora pre-suplementaria, posee un importante número de interconexiones tanto con la corteza sensoriomotora como con la corteza asociativa y con regiones del sistema límbico. Esta red de conexiones los erige como elementos clave de los circuitos cerebrales motores, cognitivos y emocionales implicados en procesos como la ejecución automática de planes motores aprendidos, el aprendizaje por reforzamiento, la implementación de conductas orientadas a metas, la selección de respuestas

competitivas, la toma de decisiones, la ejecución de contenidos de la memoria de trabajo y la propia inhibición (Jahanshahi et al., 2015). Para comprender con exactitud el papel que desempeñan estas estructuras subcorticales en este amplio abanico de conductas, resulta esencial explicitar la división funcional que existe entre los diferentes núcleos que los integran. En primera instancia, tanto el estriado como el núcleo subtalámico representarían las principales regiones de entrada al sistema de los ganglios basales, ya que serían las principales receptoras de las aferencias provenientes de la corteza cerebral. Por su parte, el segmento interno del globo pálido y la parte reticulada de la sustancia negra constituirían la puerta de salida principal del sistema. Estas dos regiones, dada su gran similitud morfo-funcional, podrían considerarse, de hecho, una sola estructura depositaria de las representaciones de las extremidades y de la cabeza y el cuello, respectivamente. El mecanismo de comunicación que rige el funcionamiento de los ganglios basales actuaría en base a un equilibrio de inhibición-desinhibición-facilitación. Así, estos núcleos de salida mantendrían a las regiones de la corteza bajo una inhibición tónica para prevenir movimientos inapropiados mediante las conexiones inhibitorias (gabaérgicas) con los núcleos ventral-lateral y ventral-anterior del tálamo que proyectarían respectivamente a la corteza motora primaria y a la corteza premotora. Así, esta conexión tónica ejercida por el denominado "freno palidal" se vería interrumpida de forma fásica por medio de la activación del estriado, normalmente silente, en respuesta al plan motor elaborado en la corteza. Esta activación del estriado eliminaría de forma selectiva el "freno palidal" inhibiendo a la puerta de salida de los ganglios basales, liberando así los correspondientes núcleos talámicos y, finalmente, desembocando en la activación de la corteza motora. Esta cascada de activación es la que se ha denominado ***vía directa del movimiento*** (Afifi, Bergman y Orizaga Samperio, 2006; Jahanshahi et al., 2015) (Figura 5).

La finalización de dicha activación y, por tanto, del movimiento, reflejaría la puesta en funcionamiento de la ***vía indirecta del movimiento*** (Afifi, Bergman y Orizaga Samperio, 2006; Jahanshahi et al., 2015) y sería consecuencia de la activación de las dos estructuras mediadoras de los ganglios basales: la sección externa del globo pálido y el núcleo subtalámico. Éste último núcleo, conectado de forma excitatoria con el tándem del globo pálido externo/sustancia negra reticulada, se vería implicado en la regulación del tono inhibidor de dicha estación de salida. Sin embargo, el núcleo subtalámico se encontraría inhibido tónicamente precisamente por el globo pálido externo. Esta región, por su parte, tendría también conexiones inhibitorias con la estación de salida del sistema y recibiría también la inhibición fásica del estriado. De este modo, la activación del estriado que desencadenaría una respuesta motora de forma rápida, a su vez desembocaría en una desactivación fásica del globo pálido externo, que consecuentemente retiraría su inhibición del núcleo subtalámico y del tándem formado por la sección interna del globo pálido y la sustancia negra. De este modo, al estar menos inhibido el núcleo subtalámico, éste excitaría con mayor intensidad a la estación de salida del sistema, que recobraría su tono inhibidor lo que, en conjunción con la retirada de la inhibición procedente del globo pálido externo, se traduciría finalmente en la terminación del movimiento. Sin embargo, el núcleo subtalámico recibiría aferencias excitatorias de un importante conjunto de regiones corticales, entre las que se encontraría la corteza motora, el área motora suplementaria, la corteza premotora

dorsal y ventral, la corteza cingulada anterior y la CPFDL. Así, la activación directa del núcleo subtalámico ocasionaría un aumento de la intensidad del "freno palidal" que en conjunto implementaría una vía rápida de ejecución del comando cortical, por lo que este circuito ha venido a denominarse como la ***vía hiperdirecta*** (Jahanshahi et al., 2015, Nambu, Tokuno y Takada, 2002) (Figura 5).

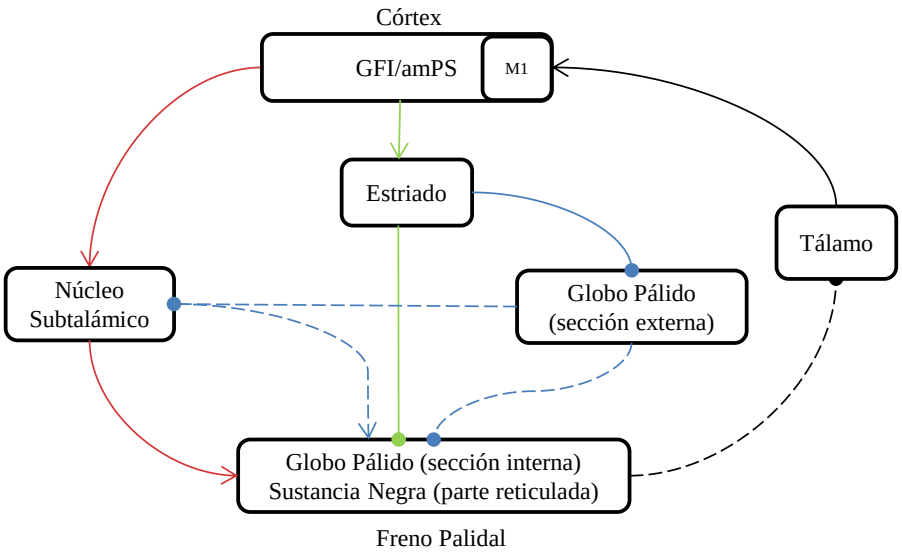

Figura 5. Circuito frontal-ganglios basales del control de respuestas. Las flechas representan conexiones excitatorias, mientras que los conectores de punta redondeada representan conexiones inhibitorias. Los colores verde, azul y rojo representan, respectivamente, las vías directa, indirecta e hiperdirecta. Las líneas discontinuas reflejan conexiones tónicas entre los elementos del circuito, mientras que las líneas continuas reflejan conexiones fásicas. GFI: Giro Frontal Inferior, amPS: área motora presuplementaria, M1: corteza motora primaria. Adaptada de Chambers, Garavan y Bellgrove (2009).

De este modo, la detallada caracterización del sistema de ejecución de respuestas motoras ha facilitado el mapeo neural de los procesos que intervienen en las tareas prototípicas de inhibición de respuesta. En concreto, se ha descrito el flujo de activación del mencionado sistema en una tarea *stop-signal* (Chambers, Garavan y Bellgrove, 2009). En primera instancia, en un ensayo *go* (de respuesta motora), se produce una activación inicial de la *vía hiperdirecta* dirigida por las áreas motoras corticales, con el objetivo de suprimir todos los programas motores a modo de señal de reseteo. En segundo lugar, la respuesta específica se libera del "freno palidal" mediante la activación de la vía fronto-estriatal directa. Finalmente, es la activación de la vía indirecta la encargada de detener el movimiento. Por su parte, en un ensayo *stop* (de inhibición motora), la *vía hiperdirecta* se reactivada mediante la conexión entre el giro frontal inferior-área motora presuplementaria y el núcleo subtalámico, constituyendo un interruptor de parada basada en el estímulo *stop*. Esta secuencia de acontecimientos sugiere que la cancelación de una respuesta se encuentra mediada tanto por la *ruta hiperdirecta* como por la *vía indirecta* o incluso por ambas simultáneamente.

Pese a la exhaustividad con la que se ha abordado el estudio de las bases cerebrales de la cancelación de respuestas motoras con el paradigma *stop-signal* en estudios con RMf, debe destacarse que el tiempo medio de inhibición estimado mediante esta tarea no supera con frecuencia los 500 milisegundos. Este hecho

coloca a otras técnicas con mayor resolución temporal, como la electroencefalografía (EEG), en una posición privilegiada para estudiar de forma más directa los correlatos neurales implicados en el proceso de cancelación de una respuesta motora (para una revisión, véase Huster, Enriquez-Geppert, Lavallee, Falkenstein y Hermann, 2013). Estos estudios se han basado en el análisis de los potenciales evento-relacionados (PERs) y las oscilaciones de los ritmos cerebrales, medidas que presentan importantes diferencias (Schneider y Maguire, 2018).

Los PERs son respuestas neurales iniciadas en el mismo momento tras la presentación de un estímulo objetivo, que emergen a partir del promediado de múltiples ensayos de una misma condición experimental. Esto contribuye a cancelar la actividad EEG no relacionada con la presentación del estímulo o cuyo momento de inicio no es común. Por tanto, los PER reflejan desviaciones de la amplitud de la señal EEG respecto a una línea base previa, de manera que la amplitud y la latencia de los máximos y mínimos de estas ondas representan indicadores de procesos sensoriales y cognitivos de carácter discreto que se despliegan a lo largo del tiempo en respuesta a ciertos estímulos (Roach y Mathalon, 2008). Por otro lado, las dinámicas oscilatorias caracterizan la evolución espectral-temporal de la actividad neural, descomponiendo la señal EEG en diferentes frecuencias cuya energía varía temporalmente. Esta descomposición se implementa en ensayos individuales que después se promedian, lo que permite detectar respuestas neurales cuyo momento de inicio no es constante respecto a la presentación del estímulo a lo largo de las múltiples frecuencias examinadas.

En el caso concreto de la inhibición de respuestas motoras, los estudios con PERs, que han empleado tareas *stop-signal* y *go/no-go* han puesto de manifiesto la estrecha relación existente entre los componentes N2 y P3 y la inhibición (Huster et al., 2013). En primera instancia, suele observarse una negatividad en los electrodos fronto-centrales en torno a los 200-300 milisegundos (N2) después de la presentación de los estímulos *no-go* o *stop*. Con posterioridad, aparece un componente positivo en torno a los 350-400 milisegundos con una topografía fronto-central (P3). Cabe destacar que la aparición de estos dos componentes no es específica de las tareas de inhibición, ya que se han visto asociados a multitud de procesos cognitivos relacionados con un amplio número de tareas experimentales diferentes (Polich, 2007; Folstein, Van Petten y Rose, 2008). Por ello, muchos han sido los intentos por concluir la especificidad de estos componentes como correlatos electrofisiológicos del proceso de inhibición.

Con respecto al componente N2, los datos de investigaciones previas no parecen asignar un papel específico en la inhibición de respuesta, ya que este componente de los PERs parece ser sensible a un amplio número de manipulaciones experimentales relacionadas con la supervisión del conflicto, las expectativas o la novedad (Enriquez-Geppert, Konrad, Pantev y Huster, 2010; Kropotov, Ponomarev, Hollup y Mueller 2011). Por su parte, existe un mayor acuerdo a la hora de considerar a P3 como el componente más relacionado con la supresión de una respuesta motora. De hecho, la amplitud de este componente parece aumentar en situaciones en las que se precisa cambiar o suprimir una respuesta (Kropotov et al., 2011) o en aquellos

contextos en los que la inhibición es más demandante (Smith, Johnstone y Barry, 2007). No obstante, al mismo tiempo también se ha planteado que la latencia del componente P3 fronto-central sería demasiado tardía como para reflejar el propio proceso de inhibición motora, ya que la estimación del tiempo medio de inhibición se estima entre los 200-270 milisegundos tras la presentación de la señal *stop*, mientras que la máxima amplitud de este componente suele registrarse en torno a los 350-400 milisegundos. Por ello, interpretaciones alternativas sugieren que este componente en realidad podría estar reflejando un efecto posterior a la inhibición, más relacionado con la propia evaluación del desempeño inhibitorio o de su resultado (Bruin, Wijers y Van Staveren, 2001). Sin embargo, el trabajo de Wessel y Aron (2015), reveló que la latencia del inicio del componente P3, definido como el punto temporal más temprano en el que podía detectarse una diferencia significativa entre los ensayos *stop* y ensayos *go*, correlacionaba con el *SSRT* de cada participante, coincidiendo así con la finalización del proceso inhibitorio. Por ello, los datos disponibles hasta el momento parecen señalar que el inicio del componente P3 sería correlato electrofisiológico fiable del propio proceso inhibitorio.

Como se ha señalado previamente, la naturaleza de la señal EEG es multidimensional. Por ello, es posible que parte de las preguntas que son difíciles de resolver estudiando únicamente las respuestas fijadas en fase a los estímulos presentados, puedan hallar respuesta empleando otros procedimientos de análisis de la señal EEG como el análisis de tiempo-frecuencia. Dado que los ritmos EEG son en sí mismos el resultado de actividad sincrónica entre y en el interior de grupos neuronales, se asume que los cambios en la energía del EEG reflejarían cambios subyacentes en la sincronía neural, por lo que precisamente se utilizan los términos de "sincronización evento-relacionada" o "desincronización evento-relacionada" para describir los cambios en la energía asociada a ciertos eventos (Roach y Mathalon, 2008).

De entre los principales ritmos responsables de la cognición humana (delta, theta, alfa, beta y gamma), la evidencia previa sugiere que dos de ellos estarían particularmente relacionados con la inhibición de respuesta. En primer lugar, uno de los efectos más comúnmente observados remite a un incremento de la energía de la banda theta en los ensayos *no-go* y *stop* en comparación con los ensayos *go*, entre los 200-600 ms que siguen a la presentación del estímulo. No obstante, al igual que el componente N2, estos incrementos de energía theta no parecen ser una respuesta específica ante este tipo de ensayos, ya que también aparecen ante niveles elevados de conflicto entre respuestas o estímulos (Nigbur, Ivanova y Stürmer, 2011). En todo caso, existe un conjunto de estudios que sugieren que el ritmo theta está implicado en la propia inhibición (Jha et al., 2015; Isabella, Ferrari, Jobst, Cheyne y Cheyne, 2015). Por otro lado, un segundo los resultados de otros estudios sugieren que la banda de frecuencia beta sería la principal dinámica oscilatoria relacionada con la inhibición de respuesta. Así, los estudios de Swan y colaboradores (2009 y 2012) encontraron incrementos de la actividad beta en el giro frontal inferior derecho y en el área motora pre-suplementaria en los ensayos *stop* mediante registros intracraneales. En este sentido, los datos convergentes acerca de los incrementos de activación registrados tanto a nivel del núcleo subtalámico (Wessel et al., 2016) como en las regiones prefrontales críticas para la cancelación de respuestas (giro frontal inferior y corteza motora pre-

suplementaria), plantearían la posibilidad de que este sistema opere en base a la comunicación en la banda de frecuencia beta.

1.4 Tipos de inhibición

Una vez delineado el marco general de resultados relativos al estudio de la inhibición de respuesta, puede matizarse que éste remitiría en realidad a una modalidad de inhibición que puede denominarse como reactiva, ya que la manera en la que se estudia en las tareas experimentales exige su emergencia en respuesta a un estímulo externo. Sin embargo, no cabe duda de que este tipo de inhibición rápida, reactiva y guiada por un estímulo no basta para explicar las dificultades conductuales que puede mostrar una persona impulsiva o un paciente con un trastorno caracterizado por altos niveles de impulsividad y desinhibición. Ello exige la extensión de este constructo hacia otras modalidades de inhibición, quizás más ajustadas a lo que se observa en contextos naturales.

Se han propuesto, por ello, otras formas de inhibición que trascienden el carácter fásico de la inhibición reactiva anteriormente mencionada. Resulta evidente que para superar cierto tipo de dificultades (tales como controlar el impulso asociado al estímulo de coger un cigarrillo en un caso de adicción a la nicotina), sería preciso un mecanismo de acción más demorada en el tiempo, que contuviese una respuesta determinada ante la detección de un conflicto entre respuestas competitivas, para tratar así finalmente de seleccionar la alternativa más ventajosa. Este tipo de inhibición ha venido denominándose *enlentecimiento inducido por el conflicto*. Más allá de esto, es posible que una persona pueda proponerse moderar o contener una respuesta incluso antes enfrentarse al estímulo o situación que la desencadena lo que se traduciría en un tipo de inhibición que se pondría en marcha por adelantado, por lo que ha recibido el nombre de *control inhibitorio proactivo*. Los estudios dirigidos a esclarecer los correlatos neurales de la inhibición proactiva señalan que la red cerebral implicada en la inhibición reactiva sería precisamente la que se encontraría activa de forma preventiva este tipo de inhibición (Aron et al., 2011). Así, un efecto comúnmente observado en el laboratorio es que los participantes que se encuentran bajo este control proactivo suelen ser más rápidos cuando deben cancelar sus respuestas de forma reactiva (Chikazoe et al., 2009; Jahfari, Stinear, Claffey, Verbruggen y Aron, 2010).

Otro criterio de distinción entre diferentes modalidades de inhibición remitiría no tanto a la dimensión temporal de su implementación, sino a su especificidad. Así, se puede distinguir entre situaciones demandantes de una *inhibición global* (quedarse paralizado ante un depredador), frente a otras que exigen una *inhibición selectiva* (parar de cantar mientras se continúa tocando el piano o interrumpir una respuesta ante cierta instrucción, pero no ante otras). De este modo, la inhibición selectiva se explora con un conjunto heterogéneo de tareas que comparten el requisito fundamental de exigir la interrupción de la respuesta ante un estímulo específico, pero no ante otros (parada selectiva a nivel de estímulo) o la detención de una respuesta en particular, pero no de otras (parada motora selectiva). Así, se ha buscado integrar la inhibición

selectiva dentro del circuito propuesto para la inhibición reactiva de una respuesta motora. No obstante, la investigación ha sido más prolija en el uso de tareas de inhibición selectiva a nivel de respuesta, cuyos datos apuntan a que sería más bien la *vía indirecta*, en lugar de la vía cortico-subtalámica, la encargada de ejercer un control selectivo de la respuesta, otorgando así un papel clave al estriado y a la sección externa del globo pálido. Por su parte, la inhibición selectiva a nivel de estímulo apenas se ha explorado hasta el momento. Dada la complejidad del contexto en el que habitualmente tiene lugar nuestra conducta, no resulta frecuente que la señal que marque la necesidad de interrumpir uno de nuestros comportamientos sea fácilmente identificada como un elemento distinguible del resto. Al contrario, lo habitual es precisar unos instantes para discriminar los estímulos que nos rodean para después ejecutar la preceptiva respuesta. La presente tesis doctoral se centrará en el estudio de los mecanismos neurales y conductuales de este tipo de inhibición selectiva.

1.5 Inhibición selectiva a nivel de estímulo

El estudio experimental de la implementación selectiva de la inhibición de respuesta se ha desarrollado a través de una modificación de la tarea *stop-signal* en la que se incluye, además de los estímulos *go* y *stop*, un tercer estímulo denominado *continuar o ignorar (continue o ignore,* en inglés: Etchell, Sowman y Johnson, 2012*).* A los participantes se les pide parar su respuesta ante la aparición de la señal stop, pero continuar su respuesta ante la señal *ignorar*. La nueva condición introducida en este paradigma *(ignorar*) trata de reproducir con la mayor fidelidad posible las características tanto estimulares como de frecuencia de aparición de la condición *stop,* exigiendo a los participantes que antes de cancelar la respuesta que habían iniciado previamente deban discriminar qué señal es la que se ha presentado, para después actuar en consecuencia. Por ello, la comparación funcional entre la condición *stop* y la nueva condición *ignorar* se presenta como una excelente oportunidad para intentar solventar las limitaciones de los contrastes típicamente empleados para examinar los mecanismos neurales específicamente relacionados con la inhibición de respuesta. Las comparaciones funcionales comúnmente empleadas para aislar el proceso inhibitorio (go-acierto vs. stop-acierto y stop-acierto vs. stop-fallo) no controlan algunos factores que difieren entre condiciones como la frecuencia de aparición de los estímulos, el número de estímulos presentados o el procesamiento cognitivo y emocional asociado al error. Estas diferencias y no las relacionadas con el propio proceso de inhibición podrían explicar, al menos, una parte de las diferencias observadas en la actividad neural (Boehler, Appelbaum, Krebs, Hopf y Woldorff, 2010; Dimoska, Johnstone y Barry, 2006; Li et al., 2006; Sharp et al., 2010).

Bisset y Logan (2014) encontraron que la mera inclusión de la condición *ignorar* en el mismo bloque de ensayos que las dos condiciones experimentales clásicas (*go* y *stop*) tenía una importante consecuencia que no había sido anticipada. Mientras que el objetivo de la incorporación de la condición *ignorar* no era otro que el de exigir a los participantes realizar una discriminación perceptiva previa a la implementación de la inhibición de respuesta, los datos conductuales de esta investigación mostraron que un grupo de los

participantes parecía resolver con éxito la tarea propuesta sin acogerse al esquema previsto de discriminación-inhibición. Así, estos autores identificaron conductualmente dos estrategias diferenciadas para resolver la tarea de inhibición selectiva a nivel del estímulo. Por un lado, un grupo de participantes resolvió la tarea siguiendo la secuencia esperada: discriminar primero la señal visual presentada (verificando así si se trata de la señal *stop* o de la señal *ignorar),* para después cancelar la respuesta previamente iniciada en caso de tratarse específicamente de la señal *stop (estrategia discriminar-parar, DP).* Por otro lado, algunos participantes cancelaron su respuesta de forma inespecífica ante la aparición de cualquier señal (*stop* o *ignorar*) tras el estímulo *go,* para después reiniciar su respuesta si la señal percibida era la de *ignorar o continuar*. Por tanto, este segundo grupo de participantes parecía invertir el orden esperado de procesos implementados durante esta tarea: primero paraban su respuesta y después discriminaban entre los estímulos (*estrategia parar-discriminar, PD*)

La identificación de estas dos estrategias para resolver una tarea *stop-signal* selectiva quedaría caracterizada en cada individuo por el patrón de diferencias observado entre los tiempos de reacción (TR) medios para cada tipo de ensayo en los que se emite una respuesta (ensayos *go-acierto,* ensayos *stop-fallo,* ensayos *continuar*). En concreto, aquellos participantes que emplean la estrategia *DP* mostrarían TR significativamente menores en los ensayos en los que ha habido un fallo inhibitorio (*stop-fallo)* en comparación con los ensayos *go-acierto* y los ensayos i*gnorar* (entre estos últimos no se observarían diferencias: TR stop-fallo<TR go=TR ignorar). Por el contrario, aquellos participantes que utilizan la estrategia *PD* mostrarían TR significativamente diferentes entre todos los tipos de ensayos (TR stop-fallo <TR go<TRignorar).

De acuerdo con este patrón de diferencias, en el primer caso, los participantes lidiarían con el ensayo *ignorar* de forma equivalente al ensayo *go,* dado que en ambos casos deben emitir finalmente la respuesta solicitada. Consecuentemente, en la estrategia *DP,* el tiempo medio de inhibición (*SSRT*) debería contener una etapa de procesamiento relacionada con la discriminación de las señales, lo que debería reflejarse en latencias superiores a las observadas en el contexto de la inhibición simple reactiva. Por su parte, en la estrategia *PD,* el tiempo medio de reacción de los ensayos de la condición ignorar serían necesariamente más lentos, posiblemente debido a la inhibición previa inespecífica que se habría ejecutado en este caso. Por ello, el tiempo medio de inhibición de estos participantes sería equiparable al del caso de la inhibición simple reactiva, ya que de hecho estarían cancelando su respuesta sin incluir ninguna etapa de discriminación en la cascada de eventos incluido en el tiempo medio de inhibición o *SSRT*.

Es importante señalar que en ambos casos se mantiene el efecto que atestigua la satisfacción del supuesto de independencia entre los procesos de respuesta (*go*) y de parada (*stop*) que rige el *modelo de carrera de caballos* propuesto originalmente por Logan y Cowan (1984). Sin embargo, Bisset y Logan (2014) observaron un patrón de diferencias más entre sus participantes. En una considerable proporción de la muestra analizada se observó que la prescriptiva diferencia entre el tiempo medio de los ensayos *stop-fallo* y

el de los ensayos *go* se reducía hasta no observarse diferencias significativas, manteniéndose un TR medio para los ensayos *ignorar* significativamente más lento que para los ensayos *go*. De esta forma, la estrategia *DP* quedaría disgregada en dos subestrategias en función de si se cumple o no el supuesto de independencia del modelo de carrera de caballos: la *estrategia DP independiente* o *Dpi* (en donde el TR stop-fallo <TRgo=TR ignorar) y la *estrategia DP dependiente o DP (*en donde TR stop-fallo=TRgo<TRignorar).

La violación del supuesto de independencia del *modelo de carrera de caballos* para los participantes que adoptan la *estrategia DPd* parecería deberse a la emergencia de algún tipo de dependencia entre el proceso de emisión de una respuesta con respecto al proceso de discriminación entre las señales de inhibición (*stop*) y continuación (*continuar*). Los autores proponen varias interpretaciones con respecto a los factores que generan esta dependencia, cada una de las cuales conllevaría importantes consecuencias con respecto a la fiabilidad de la estimación del tiempo medio de inhibición (*SSRT*). La primera de ellas plantea que esta dependencia podría estar reflejando que ambos procesos estarían consumiendo los mismos recursos, por lo que discriminar las señales podría eliminar recursos del procesamiento de la señal de respuesta. Si esta hipótesis se verificase, podría asumirse entonces que la dependencia entre el procesamiento de la señal *go* y el procesamiento de las señales *stop* y *continuar* sería la misma, por lo que el proceso de respuesta (*go)* se enlentecería en la misma medida en ambos tipos de ensayo, quedando habilitado el uso de la distribución de tiempos de reacción ante la señal de *ignorar* para calcular el tiempo medio de inhibición (*SSRT*). Sin embargo, los autores también plantean que esta dependencia podría ser consecuencia de una preparación para conseguir una meta, de manera que tanto la señal *stop* como la señal *ignorar* pudieran quedar asociados a la meta de cancelar la respuesta. De esta forma, tanto el TR de los ensayos *stop-fallo* como el de los ensayos *ignorar* se vería enlentecido. No obstante, no cabe duda de que el estímulo *stop* representaría en mejor medida a esta meta, lo que ocasionaría que el proceso *go* se enlenteciera más en los ensayos de inhibición que en los ensayos de ignorar, por lo que no podría emplearse la distribución de TR de los ensayos ignorar para calcular alternativamente el tiempo medio de inhibición. Finalmente, es posible que tanto la señal *stop* como la señal *ignorar* activen parcialmente la red de inhibición, lo que por su parte enlentecería el proceso de respuesta. Si esta hipótesis se verificase, los autores plantean que la distribución de los TR de la condición *ignorar* podrían emplearse para estimar el tiempo medio de inhibición.

Por lo tanto, ante esta evidencia, resulta indispensable controlar la estrategia que adopta cada participante al resolver una tarea *stop-signal* selectiva a nivel de estímulo para interpretar adecuadamente los datos obtenidos utilizando este paradigma experimental. Según nuestro conocimiento, los estudios que componen la presente tesis doctoral representan el primer intento por explorar los correlatos neurales asociados con las principales estrategias adoptadas durante una tarea de inhibición selectiva a nivel de estímulo. En concreto, estos estudios examinaron las posibles diferencias conductuales y electrofisiológica entre estrategias en la implementación del proceso específico de la interrupción o cancelación de una respuesta motora

2 OBJETIVOS E HIPÓTESIS GENERALES

2.1 Objetivos generales

- Examinar los correlatos electrofisiológicos (PER y oscilaciones analizados tanto a nivel de superficie como de vóxel) asociados con cada una de las estrategias empleadas para resolver una tarea de inhibición selectiva a nivel del estímulo según la clasificación realizada por Bisset y Logan (2014)

- Identificar los correlatos electrofisiológicos (PER y oscilaciones analizados tanto a nivel de superficie como de vóxel) que se relacionan de manera específica con el proceso de cancelación de una respuesta motora.

2.2 Hipótesis generales

- Se observará un patrón de actividad electrofisiológica (tanto a nivel de superficie como de vóxel) distinto para las estrategias caracterizadas por inhibir selectivamente ante la señal *stop* pero no ante la señal *ignore* (*DPi/DPd*) y la estrategia caracterizada por inhibir de manear no selectiva ante ambos tipos de señales (*PD*). En concreto, se espera que los correlatos electrofisiológicos del proceso de cancelación de una respuesta motora (N2/P3, ritmos theta/beta y giro frontal inferior/área motora presuplementaria) se observen en las estrategias *DPi/DPe* pero no en la estrategia *PD*, ya que en esta última los participantes interrumpen sus respuesta ante todas las señales presentadas.

- El inicio del componente P3, las oscilaciones en beta-alto/bajo y el giro frontal inferior/área motora presuplementaria serán los correlatos electrofisiológicos más relacionados con el proceso de cancelación de una respuesta motora, los cuales se observarán de una manera más específica en la comparación funcional entre la condición *stop-acierto* y la condición *ignorar* en las estrategias caracterizadas por inhibir selectivamente ante la señal *stop* pero no ante la señal *ignorar* (*DPi/DPd*).

3 PRIMER EXPERIMENTO

3.1 Objetivos

- Examinar los correlatos de los PER, tanto a nivel de superficie como de vóxel, implicados en la cancelación de una respuesta motora en cada una de las estrategias utilizadas para resolver una tarea de inhibición selectiva a nivel del estímulo.

- Aislar los correlatos de los PER, tanto a nivel de superficie como de vóxel, que se relacionan específicamente con el proceso de cancelación de una respuesta motora.

- Examinar si la latencia estimada del tiempo medio de inhibición *(SSRT*) para cada una de las estrategias empleadas para resolver la tarea de inhibición selectiva coincide con la latencia de los efectos de los PER vinculados con el propio proceso de cancelación de respuesta.

3.2 Hipótesis

- Los correlatos de los PER relacionados con la cancelación de una respuesta motora (N2/P3 a nivel de superficie y giro frontal inferior/área motora presuplementaria a nivel de vóxel) se observarán en las estrategias caracterizadas por inhibir selectivamente (*DPi/DPd*), pero no en la estrategia caracterizada por inhibir de manera no selectiva (*PD*).

- El inicio del componente P3 y el giro frontal inferior/área motora presuplementaria serán los correlatos de los PER más relacionados con la cancelación de una respuesta motora, los cuales se observarán de una manera más específica en la comparación funcional entre la condición *stop-acierto* y la condición *ignorar* en las estrategias caracterizadas por inhibir selectivamente ante la señal *stop* pero no ante la señal *ignorar* (*DPi/DPd*).

- La latencia estimada del tiempo medio de inhibición (*SSRT*) en las estrategias caracterizadas por inhibir selectivamente (*DPi/DPd*) no diferirá de la latencia de los efectos de los PER (mayor amplitud de P3 en condición stop-acierto vs. condición ignorar) relacionados con el proceso de cancelación de la respuesta.

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Neural and behavioral correlates of selective stopping: Evidence for a different strategy adoption

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ABSTRACT

The present study examined the neural and behavioral correlates of selective stopping, a form of inhibition that has scarcely been investigated. The selectivity of the inhibitory process is needed when individuals have to deal with an environment filled with multiple stimuli, some of which require inhibition and some of which do not. The stimulus-selective stop-signal task has been used to explore this issue assuming that all participants interrupt their ongoing responses selectively to stop but not to ignore signals. However, recent behavioral evidence suggests that some individuals do not carry out the task as experimenters expect, since they seemed to interrupt their response non-selectively to both signals. In the present study, we detected and controlled the cognitive strategy adopted by participants ($n = 57$) when they performed a stimulus-selective stop-signal task before comparing brain activation between conditions. In order to determine both the onset and the end of the response cancellation process underlying each strategy and to fully take advantage of the precise temporal resolution of event-related potentials, we used a mass univariate approach. Source localization techniques were also employed to estimate the neural underpinnings of the effects observed at the scalp level. Our results from scalp and source level analysis support the behavioral-based strategy classification. Specific effects were observed depending on the strategy adopted by participants. Thus, when contrasting successful stop versus ignore conditions, increased activation was only evident for subjects who were classified as using a strategy whereby the response interruption process was selective to stop trials. This increased activity was observed during the P3 time window in several left-lateralized brain regions, including middle and inferior frontal gyri, as well as parietal and insular cortices. By contrast, in those participants who used a strategy characterized by stopping non-selectively, no activation differences between successful stop and ignore conditions were observed at the estimated time at which response interruption process occurs. Overall, results from the current study highlight the importance of controlling for the different strategies adopted by participants to perform selective stopping tasks before analyzing brain activation patterns.

Introduction

Response inhibition, defined as the ability to suppress unwanted thoughts and actions, plays a fundamental role acting as a basement for more complex cognitive capabilities (Verbruggen and Logan, 2008). Moreover, it allows people to flexibly adapt their behavior depending on current goals. The importance of this fundamental ability emerges clearly when considering its impairment in several neurological diseases and psychiatric disorders, such as Huntington's disease (Beste et al., 2008), obsessive-compulsive disorder (Bannon et al., 2002), attention-deficit/hyperactivity disorder (López-Martín et al., 2015) or substance abuse (Fillmore and Rush, 2002; Monterosso, 2005).

In order to investigate response inhibition, several experimental tasks have been designed. In particular, the so called go-no go and stop signal paradigms have widely been used to characterize the processes involved in response inhibition (Bari and Robbins, 2013; Chambers et al., 2009; Huster et al., 2013). In these tasks, a response tendency is first induced to participants (go condition), which has to be suddenly interrupted (no-go/stop condition). As a consequence the targeted response inhibition process is triggered. However, these two tasks differ in the specific nature of inhibition: the go/no-go task demands to withhold a prepotent but not yet initiated response, whereas the stop-signal task requires cancelling an already initiated response. Specifically, in the stop-signal task participants are usually asked to make button press responses to go stimuli and to interrupt their

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responses whenever a stop-signal is presented shortly after them. The main parameter of this task is the so called *stop signal delay* (SSD), which indexes the lag between the go stimulus and the stop-signal. Crucially, the probability of committing an inhibition error can be manipulated by modifying the duration of this delay, which allows for the calculation of the *stop signal reaction time* (SSRT). This has been considered to be a precise measure of the time that takes to inhibit a response. It is important to note that SSRT is an index of the several processes involved in the successful interruption of a motor response, which at least include the encoding of the stopping stimulus and the subsequent interruption of the ongoing response (Boucher et al., 2007). This estimation relies on the assumptions made by the horse-race model proposed by Logan and Cowan (1984) that describes the relative finishing time of the go (go RT) and stop (stop-respond RT) processes. Specifically, the go RT reflects the finishing time of the go process, whereas the stop-respond RT represents go RT on those trials with stop signals in which individuals fail to inhibit the response. In order to simplify the formal model of the estimation of SSRT, it is assumed that going and stopping processes (which are both active in stop trials) are independent (Logan and Cowan, 1984; Verbruggen and Logan, 2008; see also the interactive model proposed by Boucher et al., 2007). This means that the go RT distribution does not change once go responses have been initiated in stop signal trials. Importantly, this proposal assumes that a commission error will be made when going process finishes the race before stopping process. Thus, the horse-race model predicts that mean RTs on failed stop trials should be faster than mean RTs on go trials (Logan and Cowan, 1984; Verbruggen and Logan, 2009b). Finally, the model posits that the latency of the inhibition process can be measured based on the signal-response distribution by estimating the RT that represents the 50% likelihood of emitting a response and making a subsequent subtraction of the SSD from that value.

Several fMRI studies have tried to identify the neural basis of response inhibition. The results of these studies suggest that medial frontal regions (primarily, the pre-supplementary motor area; pre-SMA), the ventrolateral prefrontal cortex (inferior frontal gyrus) and the basal ganglia are particularly involved in inhibitory control (Chikazoe, 2010; Horn et al., 2003; Li et al., 2006; Li et al., 2008; Liddle et al., 2001). Of note, the chain of processes involved in the successful inhibition of a dominant response tendency is considered to last just a few hundred milliseconds (Huster et al., 2013). Therefore, the use of techniques with a high temporal resolution -such as event-related potentials or ERPs- may be suitable to complement fMRI data by providing insights on the temporal course of the processes associated with response inhibition. In this sense, prior ERPs studies with go/no-go and stop-signal tasks have already shown that two frontocentral components -the N2 (200–400 ms) and the P3 (300–600 ms)- are of particular interest when investigating response inhibition (Albert et al., 2013; Huster et al., 2013; Ramautar et al., 2004). Although the precise functional meaning of these components is still debatable, recent evidence suggests that the onset of the P3 may be a reliable index of response cancellation processes (Dimoska et al., 2006; Kok et al., 2004; Wessel and Aron, 2015). Moreover, P3 onset latency (defined as the temporal point at which differences between stop and go trials reached significance) has been found to match the time of the end of the stop process (as measured by the end of the SSRT) in the stop-signal paradigm (Wessel and Aron, 2015). In contrast, P3 peak latency is thought to reflect evaluative and reinforcement processes, which occur once the response has been successfully interrupted (Huster et al., 2013). With respect to the N2, it is however unclear whether this component reflects response interruption or other processing stages prior to response cancellation, such as perceptual mismatch, novelty processing or conflict detection (Folstein and Van Petten, 2008).

An important theoretical question concerns the processes underlying the experimental conditions typically used in studies with stop signal tasks. Notably, conclusions on the neural basis of stopping have been mainly drawn by comparing brain activity associated with successful stop trials and successful go trials, under the assumption that these conditions essentially differ in the activation of brain networks underlying response interruption. However, several studies have criticized this contrast for not being specific enough (Albert et al., 2013; Boehler et al., 2010; Dimoska et al., 2006; Etchell et al., 2012; Li et al., 2006; Sharp et al., 2010). In this sense, it should be noted that stop and go conditions not only differ in the involvement of response cancellation mechanisms per se but also in other processes (e.g., perceptual and cognitive). To try to solve this problem, in some studies successful stop trials were compared to unsuccessful stop trials. However, this solution has shown to be too restricted, since response interruption is involved to some extent in both conditions (Boehler et al., 2010). Moreover, compared with successful stopping, inhibition failures are associated with emotional processes (e.g., frustration) and error monitoring (Li et al., 2006). Finally, according to the assumptions made by the horse-race model, failed stop trials would result from a delay in the initiation of the stopping process compared to successful stop trials. This would make successful and failed stop trials difficult to compare.

In an attempt to isolate the brain activity specifically associated with the cancellation of an already initiated response, a new condition called *ignore* (or continue) has recently been introduced in the stop-signal paradigm. Although this new control condition still differs from the stop condition in decision-making processes (the ignore condition could be less relevant to the current task program than the stop one) and learning-related processes (the ignore condition leads to fewer errors than the stop one), it minimizes the aforementioned limitations by controlling both the novelty effect and sensory properties (Albert et al., 2013; Sharp et al., 2010, Etchell et al., 2012). Specifically, the sequence of events in the ignore condition resembles that of the stop condition since both trials start with a go stimulus which is followed by a signal stimulus after a delay. However, as opposed to the stop condition, participants in the ignore condition should continue responding after the signal stimulus as if it was a go trial. Moreover, the probabilities of occurrence of ignore and stop trials are kept equal, ruling out the possibility that activation differences between these two conditions reflect novelty/oddball processing. To date, only few fMRI (Boehler et al., 2010; Sharp et al., 2010), and ERP (Etchell et al., 2012) studies have followed this new approach.

In the behavioral domain, the results of studies that included ignore trials have led to the definition of the concept of *selective inhibition* (Bissett and Logan, 2014). It refers to the implementation of an inhibition that occurs only under specific circumstances related to certain stimulus features or to the response demanded by task instructions. Specifically, the inclusion of ignore trials in the so-called *stimulus-selective stopping* task would trigger slightly different processes (e.g., perceptual discrimination between stop and ignore signal) than those involved in the simple stop signal paradigm. Remarkably, it is assumed that in the stimulus-selective stopping paradigm participants selectively interrupt their responses to stop but not to ignore signals once the signal has been discriminated. However, as we will discuss later, recent evidence suggests that some participants perform the stimulus-selective stopping task by inhibiting selectively whereas others do not (because they stop their response whenever a signal occurs -ignore or stop-, and then restart the cancelled response if the signal presented was an ignore one Bissett and Logan, 2014). Interestingly, it is possible to identify the strategy adopted by each participant to perform a stimulus-selective stopping task (whether subjects inhibit selectively or not) by comparing RTs during no signal (go), ignore and stop trials (see decision matrix in Bissett & Logan, 2014, p. 457). Moreover, the independence between going and stopping assumed by the horse-race model can be tested separately for each strategy, which provides important information to establish the validity of the SSRT calculation.

Specifically, there is evidence of three distinct strategies that can be used to accomplish a stimulus-selective stop task (Bissett and Logan, 2014): *Stop then Discriminate* (*StD*), *independent Discriminate then Stop* (*iDtS*) *and dependent Discriminate then Stop* (*dDtS*). In the *StD* strategy,

subjects inhibit an already initiated response whenever a signal occurs (either stop or ignore), and subsequently discriminate the signal (restarting the cancelled go response if the signal is an ignore). The use of this strategy is typically reflected in shorter RTs for stop compared to no-signal trials (the context independence assumption between going and stopping is therefore kept), as well as in longer RTs for ignore compare to no-signal trials (because subjects stop non-selectively to both stop- and ignore-signals, and then they have to restart the response on ignore-signal trials). Thus, participants who used the *StD* strategy might not be doing what would be expected (inhibit their responses selectively). Given that discrimination of the signal occurs after the interruption of the ongoing response, SSRTs computed for subjects who use this strategy are thought to be similar to those reported in simple stop-signal tasks. Thus, in the *StD* strategy, SSRTs can be calculated using no-signal RT distributions, as in classic stop signal tasks.

By contrast, in the *iDtS* and *dDtS* strategies, subjects discriminate the signal first (either ignore or stop) and, subsequently, they cancel the already initiated go response if the signal was a stop. By adopting these strategies, participants would be thus performing the task as expected, since they stop their responses selectively. However, while signal discrimination does not interfere with going process in the *iDtS* strategy, it does so in the *dDtS* strategy. For this reason, the context independence assumption of the horse-race model is preserved in the former but not in the latter strategy. Thus, the *iDtS* strategy is associated with shorter RTs for stop than for no-signal and with similar RTs for ignore than for no-signal. This pattern of results suggest that go processing is not affected by the requirement to discriminate the signal, which may be attributed to the fact that stop and ignore signals are easy to discriminate. Therefore, SSRTs can be calculated using no-signal RT distributions in this strategy. The *dDtS* yields similar or even larger RT for stop compared to no-signal RT, and larger RTs for ignore compared to no-signal RT. These results suggest that discriminating between stop and ignore signals slows the going process whenever a signal occurs (either stop or ignore). Therefore, a certain degree of interaction is assumed in the *dDtS* strategy, possibly because stop and ignore signals are difficult to discriminate. As a consequence, the assumption of the independent race model (Logan and Cowan, 1984) would be violated, which invalidates the commonly used method for estimating SSRTs using no-signal RT distributions.

Interestingly, Bissett and Logan (2014) showed that it is possible to induce participants to adopt any of the three strategies by modifying the relative probabilities of stop and ignore trials. Thus, the same individual could use several strategies depending on the context of the task. However, when the stop and the ignore trials are presented equally often to participants (as in previous neuroimaging studies aiming to disentangle novelty from inhibition processes), there is not a priori assumption about which of the three strategies will be adopted. Thus, brain activity found in prior fMRI and ERP studies with selective stopping tasks reflected the performance of participants that may have been adopting different strategies to complete the task. It seems therefore crucial to detect and categorize the strategy used by each subject before analyzing their brain activity. Otherwise, "some subjects may not be doing what researchers think they are doing" (i.e., inhibit selectively: Bissett & Logan, 2014, p. 457).

The main aim of this study was to examine the neural correlates of response interruption for the different strategies that participants used to accomplish a stimulus-selective stop-signal task. To fully take advantage of the precise temporal resolution of the EEG, we conducted mass univariate analyses on ERP data (Groppe et al., 2011). This approach allowed us to precisely determine both the onset and the end of the processes related to response cancellation for each strategy. Source localization techniques were also employed to estimate the neural underpinnings of the effects observed at the scalp level. Importantly, an appropriate estimation of SSRTs was computed based on integration method, taking into account the strategy adopted and its consequences for horse-race model assumptions. First, we identified and classified the strategy used by each participant following the criteria proposed by Bissett and Logan (2014). We then examined the functional comparison that better isolated the brain activity specifically associated with response interruption in each strategy (successful stop vs. go, successful stop vs. failed stop, or successful stop vs. ignore). Finally, we also considered whether or not the behavioral estimation of the precise timing of response interruption process (i.e., SSRT) matches the time course of the electrophysiological differences for each of these contrasts within each strategy.

We hypothesized that the successful stop versus ignore comparison would provide the best functional contrast to isolate activation related to response interruption. However, drawing upon recent behavioral data suggesting strategic heterogeneity in selective stopping, we also predicted that such differences would emerge in *DtS* strategies (since subjects who used the *DtS* strategies, inhibit their responses selectively to stop but not to ignore signals) but not in the *StD* strategy (since subjects who used this strategy inhibit nonselectively to both stop and ignore signal). Electrophysiological differences observed in the successful stop versus ignore contrast in *DtS* strategies would have to temporally coincide with the end of the SSRT. Finally, we hypothesized that the onset of the P3, as well as the medial and ventrolateral frontal regions locations, would be the neural correlates involved in the cancellation of an ongoing response.

Method

Participants

Fifty seven right-handed undergraduate university students, with an age range of 18–39 (mean = 21.9; SD = 3), took part in this experiment. The study was approved by the local ethics committee and informed consent was obtained from each subject prior to the experiment. All participants reported normal or corrected-to-normal visual acuity and had no history of neurological or psychiatric disorders. Eight subjects were excluded from the final analysis, two due to low overall task accuracy (<2.5 SDs below the group mean), two due to unusual slow go RTs (>2.5 SDs above the group mean), and four due to non-linear adjustment of their inhibition functions (i.e., the relationship between the probability to respond during stop trials and SSDs; see Supplementary Material 1). The probability to respond given the stop signal (i.e., make a commission error) should increment monotonically from 0 to 1 as SSD values increases (Verbruggen and Logan, 2009): stopping the ongoing response is easier if the stop signal is presented far in advance of the completion of the go response, and more difficult if the stop signal is presented closer to the completion of the go response. Therefore, non-linear adjustment of a subject's inhibition function indicates that the participant did not perform the task following task instructions (i.e., responding as soon as possible when the go stimulus was presented). The final sample thus consisted of 49 participants. All of these subjects met the binomial stop-signal distribution criterion, reporting a 0.5 probability of stopping the ongoing response. As described in detail later, participants were divided according to the cognitive strategy used to perform the experimental task. The results of these analyses indicated that 30 subjects employed the *StD* strategy, whereas 19 subjects used the *dDtS* strategy. The two groups were matched for age ($t(47) = -0.066$, $p > 0.05$) and gender ($\chi^2 = 0.138$, $p > 0.05$).

Behavioral task

Participants performed a stimulus-selective stop signal task with three different stimuli: go, stop and ignore (Fig. 1). These stimuli consisted in three geometrical shapes colored in white against a black background (an arrow, a square and a diamond). Subjects were instructed to press either the left key arrow or the right key arrow in a keyboard with their respective index finger whenever an arrow pointing to any of these two orientations was presented (go trial). In

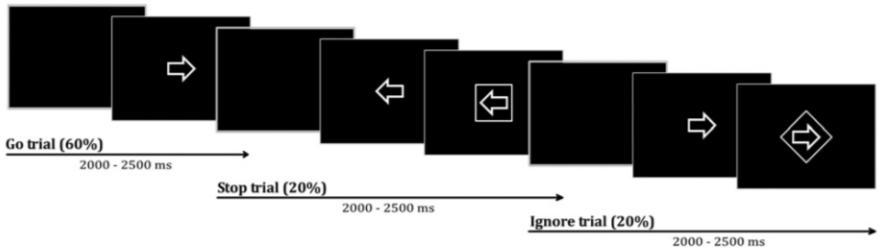

Fig. 1. Schematic representation of the stimulus-selective stop signal task.

addition, they were informed that in some trials they had to stop their response when seeing a square surrounding the arrow (stop trial), but to continue responding if a diamond was presented around the arrow (ignore trial). Critically, we insisted them to respond as fast and accurate as possible on go and ignore trials, and as accurate as possible on stop trials, trying to interrupt their ongoing responses. Subjects were instructed not to wait for the square or diamond to appear, since this behavior would compromise the assumptions in which task parameter estimations were based (Verbruggen et al., 2013). These instructions were presented to the participants on the computer monitor at the beginning of the experiment. Also, task instructions were verbally reminded to participants between blocks.

The whole task consisted of 1000 trials grouped into four blocks, each containing 250 trials (150 go, 50 stop and 50 ignore). This number of trials was determined based on a priori power analysis (see Supplementary Material 2 for further details). Each trial began with a black screen. The duration of this black screen varied randomly between 500 and 1000 ms. Thereafter, a go stimulus was presented. Arrows randomly pointed to the left or to the right in a half of the trials. In 20% of the trials (50 trials per block), the stop signal was presented after a variable delay (SSD). This delay was initially set at 200 ms, and was dynamically adjusted from stop trial to stop trial according to the individual performance of each participant. After a successful inhibition, the SSD was increased (+50 ms), which gave some advantage to the go process and reduced the probability of a successful inhibition in the next stop trial. If a response was emitted in the last stop trial, the SSD decreased (−50 ms), so stop process started earlier and the probability of a response interruption in the next stop trial increased. This staircase algorithm was applied to achieve 0.5 probability of responding to a stop signal (Levitt, 1971). In another 20% of the trials (50 trials per block), the ignore stimulus was presented after the go stimulus. The delay was also initially fixed to 200 ms, but importantly, the ignore signal delay (ISD) was equated to the most recent SSD. Thus, the adaptive adjustment of SSD was never applied after an ignore trial. In the remaining trials (60%), only go stimuli were presented (150 trials per block).

Participants carried out the experimental task seated comfortably in a darkened and sound attenuated chamber. Task stimuli were presented on a computer monitor that was positioned at eye level about 65 cm in front of the participant. The stimuli were displayed on a 19-in. LCD-LED Samsung 943 N color monitor with a 75-Hz refresh rate, a 5:4 aspect ratio, and a resolution of 1024 × 768. Before the beginning of the experimental blocks, subjects completed a practice block of 100 trials to ensure that they understood task instructions (60 go, 20 stop and 20 ignore trials; initial SSD = 200 ms). The task was designed and implemented in MATLAB, using Psychtoolbox (www.psychtoolbox.org). The Matlab script of stop-it (Verbruggen et al., 2008) served as starting point for programming our stimulus-selective stop-signal task.

EEG recording

Electroencephalogram (EEG) activity was recorded from 62 electrode locations mounted in an electrode cap (Quick-Cap, Neuroscan, Inc., USA), arranged according to the International 10–10 system. All electrodes were referenced to the average of mastoids. Bipolar horizontal and vertical electrooculograms (EOGs) were also recorded to monitor eye movements and blinks. Electrode impedances were kept below 10 kΩ. Recordings were amplified using Neuroscan SynAmps amplifiers, continuously digitized at a sample rate of 1000 Hz, and filtered online with a frequency band-pass of 0.01–100 Hz.

Data analysis

Behavioral analysis

Each subject's strategy was determined by comparing their mean no-signal (go) RT, stop-respond RT (incorrectly executed responses on stop-signal trials) and ignore RT (correctly executed response on ignore-signal trials), following the procedure described by Bissett and Logan (2014). Participants were classified as using the *iDtS* strategy (stop-respond RT < no-signal RT ≯ ignore RT), *StD* strategy (stop-respond RT < no-signal RT < ignore RT) or *dDtS* strategy (stop-respond RT ≯ no-signal RT < ignore RT). Bayes Factor was used to compare the evidence for and against the null hypotheses without bias (Rouder et al., 2009). The Bayes factor is a ratio that contrasts the likelihood of the data fitting under the null hypothesis with the likelihood of fitting under the alternative hypothesis. A Bayes factor of 1 means that the odds in favor of the null hypothesis are no better than the odds against it. Bayes factor was computed by calculating the mean and standard deviations of no-signal, stop-respond, and ignore RTs separately for each subject. Subsequently, we calculated two independent samples t tests comparing stop-respond RT with no-signal RT and ignore RT with no-signal RT, respectively. Rouder's Bayes factor calculator on the Perception and Cognition Lab website (http://pcl.missouri.edu/bf-two-sample) was used to convert t tests and sample sizes to Bayes factors. The recommended Jeffrey-Zellner-Slow Prior with the default value of 1 was used, which is appropriate if there are no strong prior assumptions (Rouder et al., 2009).

SSRTs were computed via the integration method since it has been shown to be less biased than the traditional mean method when the normality criterion in the go RT distribution is violated (Verbruggen et al., 2013). We computed SSRTs over both go and ignore RT distributions, as recommended by Bissett and Logan (2014) when dealing with these strategies. Notably, the independence assumption made by the horse-race model is violated in the d*DtS* strategy, so calculating SSRT using the go RT distribution as the underlying go distribution on stop trials is an invalid method. As Bissett and Logan (2014) have suggested, a possible solution to this problem is to use the ignore RT distribution to calculate SSRT in this strategy. However, it is worth mentioning that that this procedure might be valid only under some assumptions that have not been yet tested. Therefore, SSRTs computed using the ignore RT distribution for the subjects who adopted the *dDtS* strategy should be interpreted with caution until being validated.

ERP analysis

EEG data were processed offline using EEGLAB v.12.01 toolbox (Delorme and Makeig, 2004) implemented in MATLAB (Mathworks,

Inc.). Recordings were down-sampled to 500 Hz and filtered between 0.3 and 30 Hz using a basic FIR filter (12 dB/oct. roll-off). The continuous EEG was divided in 1400 ms epochs from 500 ms before to 900 ms after the presentation of the stimuli (go, stop or ignore). Baseline correction was made using the 500-ms period prior to the onset of stimulus. Failed go and failed ignore epochs were discarded from further analysis (go and ignore trials in which subjects did not press any key or pressed a wrong key of the keyboard). Thus, the following epochs were selected for analyses: successful go (go trials in which participants pressed the key corresponding to the arrow presented in the screen), successful ignore (ignore trials in which participants pressed the key corresponding to the arrow presented in the screen), successful stop (stop trials in which subjects did not press any key) and failed stop (stop trials in which subjects pressed a key). Stop and ignore epochs where a response was emitted before signal presentation were discarded. Independent component analysis (ICA) was then used to remove ocular and other artifacts from individual EEG data sets (Jung et al., 2000). Artifact-related independent components were carefully visually inspected. After the ICA-based removing process, visual inspection of individual EEG epochs was also conducted. If any artifact was still present, the corresponding trial was discarded too.

According to the assumptions made by the horse-race model, successful stop and failed stop conditions would not be directly comparable because of differences in the timing of the process initiation, given that failed stop RTs correspond to those stop trials in which the go process was faster than the stop process. Similarly, a response is successfully interrupted in successful stop trials because the go process is slower than the stop process, so the direct comparison between successful stop and go conditions (using all go trials) could also differ because of initiation timing differences between these two conditions. In order to reduce such processing speed differences, we selected for each subject those failed stop trials with longer RTs than his/her mean stop RT (thus establishing the slow failed stop condition) and those successful go trials with longer RTs than his/her mean stop RT (forming the slow go condition). These new two conditions were compared with the successful stop condition in each strategy.

The artifact rejection, exclusion of incorrect or miss trials, and selection of temporally matched go and stop failed trials led to the average admission of 245.7 (SD = 24.97) successful go trials, 176.2 (18.30) successful ignore trials, 94.4 (13.97) successful stop trials, and 38.9 (7.16) slow failed stop trials. Average ERPs were then computed for each subject ($n = 49$) in the four experimental conditions: successful stop, ignore, slow failed stop and slow go. Finally, ERPs were grand-averaged for these conditions for each group, depending on the strategy followed by participants (30 subjects used the *StD* strategy, whereas 19 employed the *dDtS* strategy).

Scalp-level analysis. One of the main advantages of the ERPs technique is its utility to identify the precise moment in which different neural responses to a given stimulus emerge. Mass univariate analysis (Groppe et al., 2011) arises as one of the most accurate analysis when specifying the onset and offset of significant effects whenever they occur, thereby capitalizing the high temporal resolution of ERPs. This exhaustiveness let the method to operate without any ad hoc assumption, being completely blinded to experimenter expectations. Specifically, mass univariate analysis reports the differences between ERPs associated to each experimental condition in every single electrode and temporal point as a *t-score*. Each *t-score* represents the result of performing a *t-test* in each time point and electrode. The greater *t score*, the more accurate the difference between conditions is. In order to detect ERP differences between conditions, electrophysiological activity was submitted to a within-subject permutation test based in *tmax* statistic (Blair and Karniski, 1993, $p < 0.05$ bilaterally corrected for multiple comparisons). Based on previous ERPs evidence using the stop-signal task (Etchell et al., 2012; Kok et al., 2004), a 301 points window was selected between 100 and 700 ms after stimulus presentation. Notably, the main ERP responses associated with go, ignore and stop stimuli have been observed in this time interval (Etchell et al., 2012). Thus, all temporal points comprised between 100 and 700 ms in all 62 electrodes (62×301 points = 18.662 comparisons) were included in the analyses. These point-by-point and scalp-wide analyses were performed comparing successful inhibition with the other conditions (i.e., slow go, ignore and slow failed stop) in each strategy.

Source-level analysis. To three-dimensionally locate the cortical regions underlying the experimental effects observed at the scalp level, exact low-resolution brain electromagnetic tomography (eLORETA: http://www.uzh.ch/keyinst/loreta.htm) was used. eLORETA is a 3D, discrete linear solution for the EEG inverse problem (i.e., computing 3D, functional images of electric neural activity from the scalp EEG data: Pascual-Marqui, 2007; Pascual-Marqui et al., 2011). Solutions provided by EEG-based source-location algorithms should be interpreted with caution due to their potential error margins. However, it should be noted that LORETA solutions have shown good correspondence with those provided by hemodynamic techniques, such as fMRI, in the same tasks (Dierks et al., 2000; Mulert et al., 2004; Pascual-Marqui, 2002; Pizzagalli et al., 2003). In its current version, eLORETA can compute the current density for each subject and condition at each of the 6239 voxels (voxel size: $5 \times 5 \times 5$ mm) localized in the cortical grey matter of the digitized Montreal Neurological Institute (MNI) standard brain. Within each strategy, the voxel-based whole-cortex eLORETA-images were compared between successful inhibition and each of the other conditions (slow go, ignore and slow failed stop) for the time points where mass univariate analysis showed significant differences on each comparison. These voxel-based within-group analyses were performed using the non-parametric mapping (SnPM) tool, as implemented eLORETA. As explained by Nichols and Holmes (2002), the nonparametric methodology inherently avoids problems derived from multiple comparison and does not require any assumption of Gaussianity. Voxels that showed significant differences between conditions (one-tailed $p < 0.05$) were located in anatomical regions and Brodmann areas (BAs).

Results

Behavioral results

As explained before, the strategy followed by each participant was estimated by comparing their mean no-signal (go) RT, stop-respond RT and ignore RT. The result of these analyses indicated that none of the subjects adopted an *iDtS* strategy to perform the task. Evidence for the use of the *StD* strategy was found in 30 out of the 49 subjects. Therefore, the remaining 19 subjects used a *dDtS* strategy. Repeated measures t-tests performed at group level corroborated this individual distinction. In the *StD* group, mean stop-respond RT were faster than mean no-signal RT ($t(29) = 7.785$, $p < 0.05$, Cohen's $d = 1.843$), and mean ignore RT were slower than mean no-signal RT ($t(29) = -13.729$, $p < 0.05$, Cohen's $d = 2.79$). The group that adopted a *dDtS* strategy showed mean stop-respond RT that were no significantly slower than mean no-signal RT ($t(18) = -1.805$, $p > 0.05$), and mean ignore RTs that were slower than mean no-signal RTs ($t(18) = -20.09$, $p < 0.05$, Cohen's $d = 4.723$). Their cumulative distributions are represented in Fig. 2. It should be noted that, our analyses revealed that three subjects used an *iDtS* strategy, but all of them were discarded by the aforementioned behavioral exclusion criteria, which suggested an inadequate fulfillment of task instructions. Means and standard deviations RTs across strategies are shown in Table 1.

SSRTs over both go and ignore distributions were computed for each strategy using the integration method (means and SD are shown in Table 1), knowing that this computation was only strictly valid for the *StD* strategy (Bissett and Logan, 2014). As expected, SSRTs computed using go RTs and ignore RTs in the *StD* group were faster than

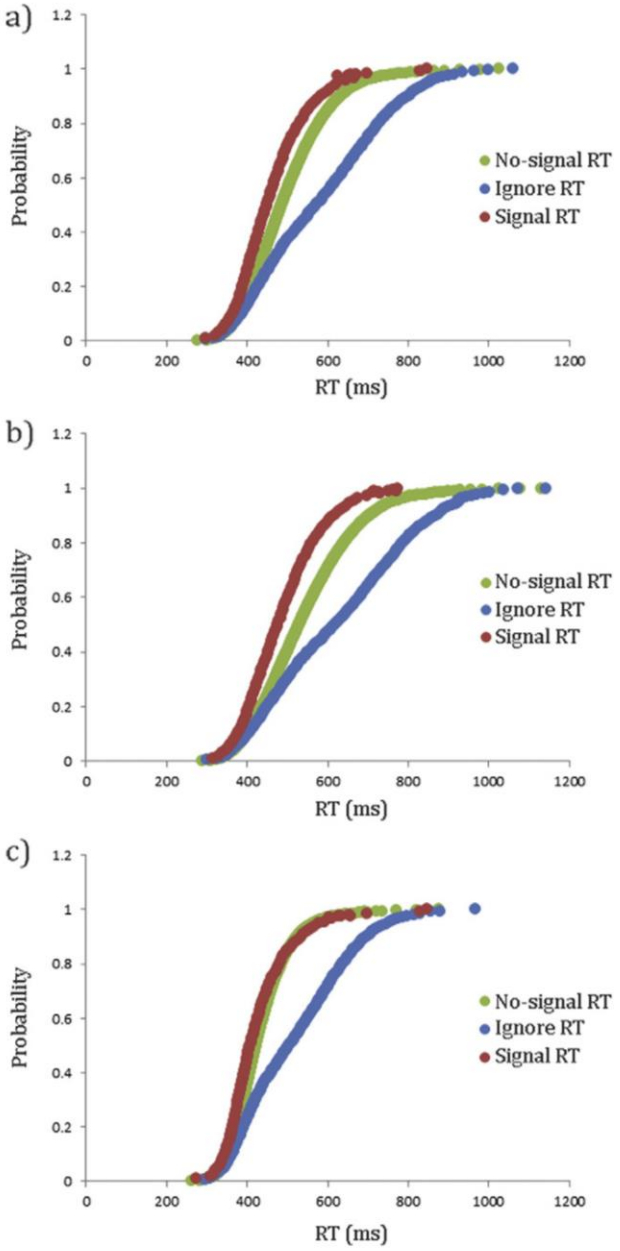

Fig. 2. Cumulative distribution functions of RT for signal-respond trials, no-signal trials, and ignore trials for all subjects (a), subjects who adopted the *Stop then Discriminate* strategy (b), and subjects who adopted the *dependent Discriminate then Stop* strategy (c).

corresponding SSRTs in the *dDtS* group ($t(47) = -2.019$, $p < 0.05$, Cohen's $d = 0.57$, and $t(47) = -2.955$, $p < 0.05$, Cohen's $d = -0.86$, respectively).

ERP results

StD strategy

Successful stop vs. slow go. Fig. 3a shows the electrodes and the temporal points where significant differences were observed in the ERPs activity elicited by successful stop and successful go conditions. A critical t score of ± 3.914 via a permutation test procedure that guarantees a 5% chance of making one or more false discoveries was derived in the entire set of 18,662 t tests. Thus, any temporal point in each of the electrode locations showing values higher than this critical t score was considered significant. The mass univariate analysis reported greater amplitudes for the successful stop condition compared to the slow go condition in all scalp electrodes between 208 and 584 ms. This time window roughly corresponds to the timing of the P3 component found in other studies (Albert et al., 2013; Huster et al., 2013; Ramautar et al., 2004). More precisely, differences started at frontal electrodes around 208 ms. They early expanded to central regions and thereafter to posterior electrodes, eventually spreading through all scalp locations around 300 ms. Fig. 3b shows a representative electrode in which differences between stop and slow go conditions are clearly noticeable.

Source localization analysis showed greater activation in the successful stop condition compared to the go condition in a large number of brain regions, including parietal, frontal, anterior cingulate, insula and temporal areas (BAs 2, 13, 4, 32, 40, 8, 6, 24, 9, 46, 7 and 42) (log-F ratio = 1.883, $p < 0.05$; 121 significant voxels). These effects were observed in the time window (208–584 ms) where statistical differences were found at the scalp level as a result of the mass univariate analysis.

Successful stop vs. slow failed stop. Fig. 4a shows the electrodes, as well as the temporal points where significant differences were observed in the pattern of ERPs activity elicited by successful stop and slow failed stop trials. The results of the mass univariate analysis showed enhanced amplitudes for the successful stop compared to the slow failed stop condition between 192 and 252 ms (critical t score = ± 4.221), which roughly corresponds to the beginning of the P3 component. Concretely, differences started at fronto-central around 192 ms. Significant differences vanished slightly before the P3 component peaked. Fig. 4b displays a representative electrode in which differences between successful stop and failed stop conditions are evident.

Source localization analysis failed to reveal significant differences between these conditions (log-F ratio = 1.129, $p > 0.05$) in the time window in which effects were observed at the scalp level (i.e., 192–252 ms).

Successful stop vs. ignore. Fig. 5a shows the electrodes and the temporal points where significant differences were observed between ERPs associated with the successful stop and ignore conditions. The mass univariate analysis reported greater amplitudes for the successful stop compared to the ignore condition, particularly in central and posterior scalp electrodes between 330 and 496 ms (critical t score = ± 4.1622). These differences were observed just after the peak of the P3 component. In particular, differences started at parieto-occipital electrodes around 330 ms, reaching the most significant values around 380 ms when all electrodes (with the exception of the most frontal ones) reported t scores greater than the critical t score. Fig. 5b

Table 1
Sample characteristics and task performance of study participants (means and standard deviations).

N	dDtS strategy	StD strategy
	19 (13 females)	30 (22 females)
Age (years)	22.1 (2.33)	22.17 (3.59)
No-signal (go) RT (ms)	462.25 (29.96)	538.91 (50.79)
Signal (stop) RT (ms)	471.35(23.27)	481.93 (22.68)
Ignore RT (ms)	581.98(36.06)	613.13 (37.17)
SSRTgo (ms)	299.79 (60.37)	268.91 (46.35)
SSRTignore (ms)	394.22 (54.24)	348.28 (52.27)
Mean SSD (ms)	166.11 (31.22)	306.35 (77.52)

Abbreviations: dDtS, dependent Discriminate then Stop strategy; StD, Stop then Discriminate strategy; RT, reaction times; SSRT, stop signal reaction times; SSRTgo, SSRT computed on the go distribution using the integration method; SSRTignore, SSRT computed on the ignore distribution using the integration method. Mean SSD, mean stop signal delay.

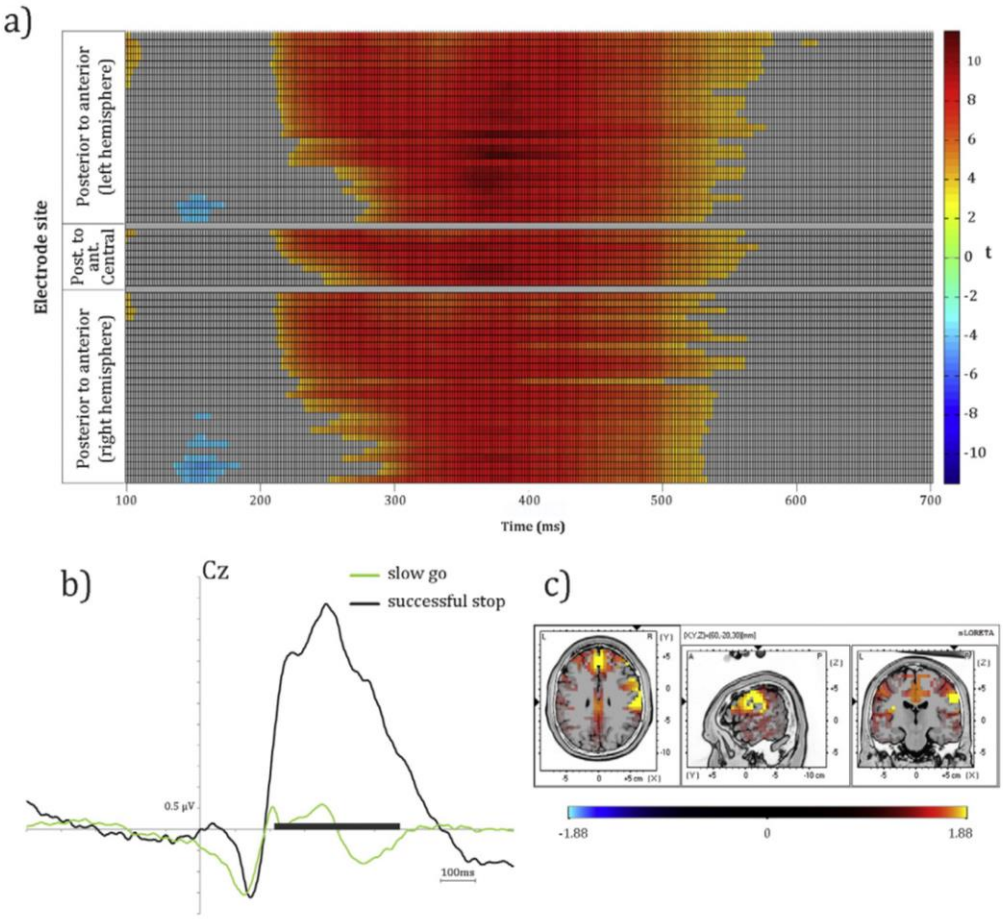

Fig. 3. Results of the mass univariate analysis. The diagram shows significant scalp ERP differences between successful stop and slow go conditions in the *Stop then Discriminate* (*StD*) strategy according to a tmax permutation test. Red and blue boxes indicate electrodes/time points in which the electrophysiological activity for the successful stop condition was greater or smaller than for the go condition, respectively. Grey boxes indicate electrodes/time points in which no significant differences between conditions were found. b) Grand ERP averages at Cz electrode where differences between conditions are clearly visible. Black color bar reflects the temporal points that showed significant differences according to mass univariate analysis. c) Source localization analysis showing increased activation during successful stop relative to go condition. Color bar represent voxels t values (log-F ratio = 1.88, $p < 0.05$).

shows a representative electrode in which differences between stop and ignore condition are clearly visible.

Source localization analyses revealed greater activation in the successful stop compared to the ignore condition (Fig. 5c). This activation was restricted to posterior brain areas, including occipital and posterior parietal cortices (log-F ratio = 1.157, $p < 0.05$; 107 significant voxels, located in BAs 18, 17, 31, 19, 39, 40). These differences were observed in the time window (330–496 ms ms) where statistical differences were found at the scalp level.

dDtS strategy

Successful stop vs. slow go. Fig. 6a shows electrodes and temporal points where significant differences were observed between the electrophysiological activity elicited by the successful stop and the go conditions. The ERP mass univariate analysis revealed larger P3 amplitudes for successful stop compared to go trials between 382 and 582 ms (critical t score: ±4.4608) in almost all electrodes. Specifically, differences started at central electrodes and subsequently spread to the whole scalp. Fig. 6b shows a representative electrode in which differences between stop and go condition are clearly noticeable.

As illustrated in Fig. 6c, source localization analyses showed greater activation in the successful stop compared to the go condition (log-F ratio = 2.089, $p < 0.05$; 504 significant voxels). This activation was observed in parietal and frontal areas (BAs 5, 7, 1, 2, 40, 3, 31, 4 and 6). These differences were observed in the same time window (382–582 ms) where statistical differences were found at the scalp level.

Successful stop vs. slow failed stop. Fig. 7a shows the electrodes and temporal points where significant differences were observed between ERPs associated with the successful stop and the failed stop conditions. As can be observed, the results of the mass univariate analysis showed enhanced P3 amplitudes for the successful stop compared to the failed stop condition between 342 and 390 ms (critical t score = ±4.7594).These temporal points were first localized in centro-parietal scalp electrodes at approximately 342 ms after stimulus presentation. Fig. 7b displays a representative electrode in which differences between successful stop and failed stop conditions are evident.

Source localization analysis failed to reveal significant differences between these conditions (log-F ratio = 2.270, $p > 0.05$) in the time window in which effects were observed at the scalp level (342–390 ms).

Successful stop vs. ignore. Fig. 8a shows electrodes and temporal points where significant differences were observed between the ERPs pattern

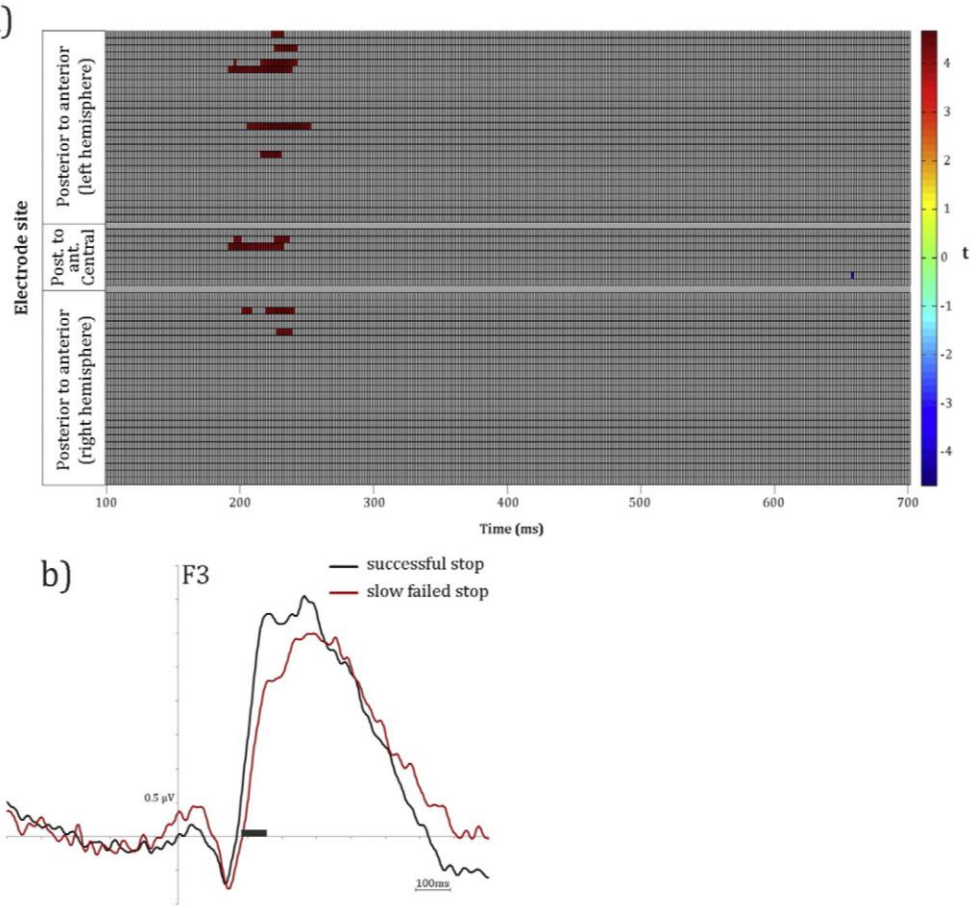

Fig. 4. a) Results of the mass univariate analysis. The diagram shows significant scalp ERP differences between successful stop and slow failed stop conditions in the *Stop then Discriminate* (*StD*) strategy according to a tmax permutation test. Red and blue boxes indicate electrodes/time points in which the electrophysiological activity for the successful stop condition was greater or smaller than for the failed stop condition, respectively. Grey boxes indicate electrodes/time points in which no significant differences between conditions were found. b) Grand ERP averages at F3 electrode where differences between conditions are clearly visible. Black color bar reflects the temporal points that showed significant differences according to mass univariate analysis.

elicited by successful stop and ignore trials. The results of the mass univariate analysis reported enhanced amplitudes for successful stop compared to successful ignore trials between 416 and 484 ms (critical t score = ±4.9311). The onset of statistical differences between these two conditions was observed prior to the peak of P3. These differences vanished at its peak. Specifically, differences were more evident in parietal (PO3, PO4, PO6) and frontal electrodes (FPZ, FP1, FC3, FC5). Fig. 8b displays a representative electrode in which differences between the stop and the go condition are clearly visible.

Fig. 8c illustrates the greater activation found for the successful stop compared to the ignore condition (log-F ratio = 1.140, $p < 0.05$; 120 significant voxels). This activation was primarily located over the middle frontal gyrus (BAs 46/9/8) and the inferior frontal gyrus (BAs 45/44). Apart from these areas, the insula (BA 13) and superior parietal regions (BA 7) were also activated in this comparison. These differences were observed in the time window (416–484 ms) where statistical differences showed significance at the scalp level.

Relationship between behavioral and electrophysiological results

To provide further support for the interpretation of neural activation results, we examined whether the estimated latency of the end of the stop process (i.e., SSRT) matched the timing of the electrophysiological differences elicited by each functional comparison within in each strategy. Specifically, we carried out one sample t tests to compare the estimated SSRTs and the earliest time point at which statistically significant differences between the successful stop condition and the other conditions was observed. Importantly, SSRTs computed over go distributions were used for the *StD* strategy, since independence assumptions between stop and go process were preserved. Alternatively, SSRTs computed over ignore RT distributions were employed in the *dDtS* strategy, since the interaction between the discrimination stage and the go process produced a dependence effect that violated the assumptions of the independent race model, discouraging the use of go RT distributions (Bissett and Logan, 2014; Logan and Cowan, 1984). In the *StD* strategy, we found significant differences between the SSRT (268.91 ± 46.35 ms) and the time at which electrophysiological differences emerged in the successful stop versus slow go (208 ms; $t(29) = 7.198$, $p < 0.05$, Cohen's $d = 1.31$), successful stop versus slow failed stop (192 ms; $t(29) = 10.034$ $p < 0.05$, Cohen's $d = 1.66$) and successful stop versus ignore comparisons (330 ms; $t(29) = -7.219$ $p < 0.05$, Cohen's $d = 1.31$). By contrast, in the *dDtS* strategy, there were no significant differences when comparing the SSRT (394.22 ± 54.24 ms) with the time at which electrophysiological differences emerged in the successful stop versus slow go (382 ms; $t(18) = 0.982$, $p > 0.05$) and successful stop versus ignore contrasts (416 ms, $t(18) = -0.1750$, $p > 0.05$). However, significant differences were observed in this strategy between the point at which

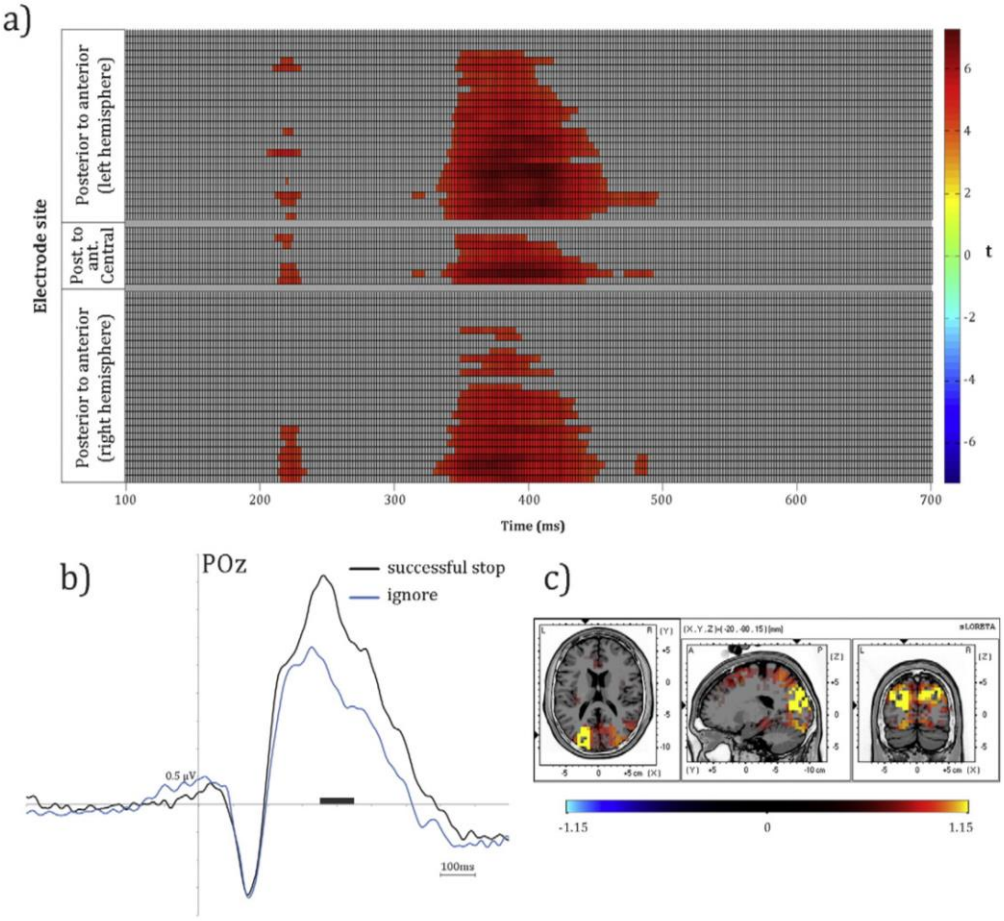

Fig. 5. a) Results of the mass univariate analysis. The diagram shows significant scalp ERP differences between successful stop and ignore conditions in the *Stop then Discriminate* (*StD*) strategy according to a tmax permutation test. Red and blue boxes indicate electrodes/time points in which the electrophysiological activity for the successful stop condition was greater or smaller than for the ignore condition, respectively. Grey boxes indicate electrodes/time points in which no significant differences between conditions were found. b) Grand ERP averages at POz electrode where differences between conditions are clearly visible. Black color bar reflects the temporal points that showed significant differences according to mass univariate analysis. c) Source localization analysis showing increased activation during successful stop relative to go condition. Color bar represent voxels t values (log-F ratio = 1.15, $p < 0.05$).

successful stop and slow failed stop conditions started to differ and SSRT (342 ms; t(18) = 4.197, $p < 0.01$, Cohen's $d = 0.96$).

Discussion

In the current study we investigated for the first time the neural basis of selective stopping by categorizing the strategy that participants adopted to perform the task. We exploited the high temporal resolution of the ERPs by using an analytical approach that allowed us to accurately determine the timing (both the onset and the end) of the response interruption processing stage for each strategy and functional comparison. Also, by using source localization methods we identified the brain regions underlying the electrophysiological differences observed at the scalp level.

With the purpose of isolating the neural correlates of response inhibition, previous brain activation studies identified several limitations of the classical stop-signal paradigm (Boehler et al., 2010; Dimoska et al., 2006; Li et al., 2006; Sharp et al., 2010). In order to overcome these constraints, the inclusion of an additional control condition (called ignore or continue) has been recommended (Etchell et al., 2012; Sharp et al., 2010). The usefulness of the successful stop versus ignore comparison relies on the theoretical assumption that the immediate initiation of motor responses is equally triggered by both ignore and go trials. However, recent empirical evidence has questioned this claim. In this sense, it has been reported that some subjects prefer to stop their response to both stop and ignore signals (*StD* strategy) instead of stopping selectively to stop signals (*DtS* strategies). Although this choice is not directly evident, it can be estimated by analyzing several behavioral parameters (Bissett and Logan, 2014).

Identification and classification of the strategy used by participants

We first identified the strategy adopted by each subject to successfully perform the stimulus selective task before comparing brain activation between conditions. For this purpose, we analyzed the RTs associated with no-signal, stop and ignore trials for each subject, following the procedure developed by Bissett and Logan (2014). The results of these analyses showed that 30 out of 49 participants adopted the *StD* strategy (61%), with the remaining 19 participants (39%) adopting the *dDtS* strategy. This ratio slightly contrasts with that reported by Bissett and Logan (2014). These authors reviewed eight experiments that used selective stopping tasks, and found that 30% of 157 participants chose the *StD* strategy whereas 59% of them adopted the *dDtS* strategy.

It might be speculated that the perceptual similarity of signals (stop and ignore) could bias a specific strategy adoption. In most studies using ignore trials, stop signals could be discriminated on the basis of color

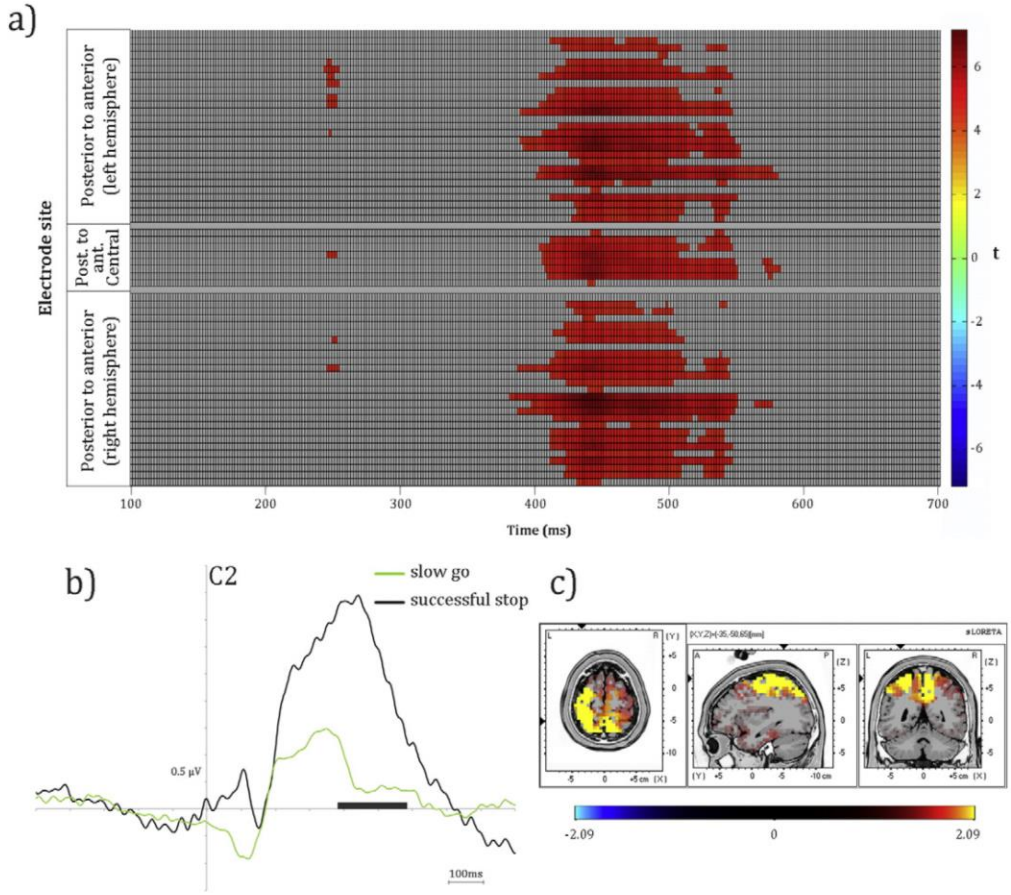

Fig. 6. a) Results of the mass univariate analysis. The diagram shows significant scalp ERP differences between successful stop and slow go conditions in the *dependent Discriminate then Stop* (*dDtS*) strategy according to a tmax permutation test. Red and blue boxes indicate electrodes/time points in which the electrophysiological activity for the successful stop condition was greater or smaller than for the go condition, respectively. Grey boxes indicate electrodes/time points in which no significant differences between conditions were found. b) Grand ERP averages at C2 electrode where differences between conditions are clearly visible. Black color bar reflects the temporal points that showed significant differences according to mass univariate analysis. c) Source localization analysis showing increased activation during successful stop relative to go condition. Color bar represent voxels t values (log-F ratio = 2.09, $p < 0.05$).

properties (usually green and red, respectively; see e.g., Sharp et al., 2010). Thus, participants may have experienced less difficulty to perform judgments that rely on a property which they could easily differentiate. As a consequence most of them would prefer to discriminate stop and ignore stimuli first and, subsequently, to inhibit or emit their response in order to efficiently follow task instructions (i.e., they use a *dDtS* strategy). By contrast, we attempted here to reduce differences between stop and ignore stimuli by using perceptually similar geometric shapes that only differed in its orientation (square and diamond). Therefore, some of our participants might have adopted a more conservative strategy when dealing with stop and ignore trials since stimuli signaling stop and ignore responses were difficult to discriminate (i.e., a *StD* strategy). Under this circumstance, to stop whenever a new stimulus occurs at the expense of having to reinitiate responses to ignore trials might be an efficient strategy to achieve task requirements more accurately.

In line with previous literature (Bissett and Logan, 2014), no evidence of the use of the *iDtS* strategy was observed, even though this would be the expected strategy from a theoretical point of view. Of note, three subjects adopted this strategy. However, they reported unexpected slow no-signal RTs and no-linearity in their inhibition functions, so their data could not be included in the analyses (see Supplementary Material 1).

Since the sequence of trial presentation was randomized for each subject, it could be possible that go trials always proceeded ignore and stop trials and some subjects became aware of this (e.g., those who used the *dDtS* strategy). Therefore, these participants could have adjusted their RTs by not following any of the aforementioned strategies. However, this possibility seems unlikely after examining the percentage of go trials that proceeded ignore and stop trials, which was approximately 60% for each of the two trials in both strategies (Supplementary Material 3). Another concern to be discussed is whether identification and decision processes in go trials (i.e., pressing the left key arrow or the right key arrow with the corresponding index finger whenever an arrow pointed to any of these two orientations) could have an effect on the sequence of processing stages involved in the task and/or the strategy adopted by participants. Given the lack of previous studies examining the neural underpinnings associated with each strategy in selective stopping, we used both left and right buttons to avoid any potential laterality bias. This allowed us to fully explore the neural basis of selective inhibition. Also, we aimed to keep our design close to the studies by Bissett and Logan (2014) and Logan and Cowan (1984). However, it is worth discussing whether difficulties in the identification of go trials delayed the initiation of the going processes. If this was the case, we could not rule out the possibility that stop processes started the race even before go processes were triggered. Nonetheless, this possibility seems unlikely in the current study since choosing between right and left responses is a simple decision that does not take much time from participants. It will be important for future studies to determine how the identification of go trials influences the timing of those

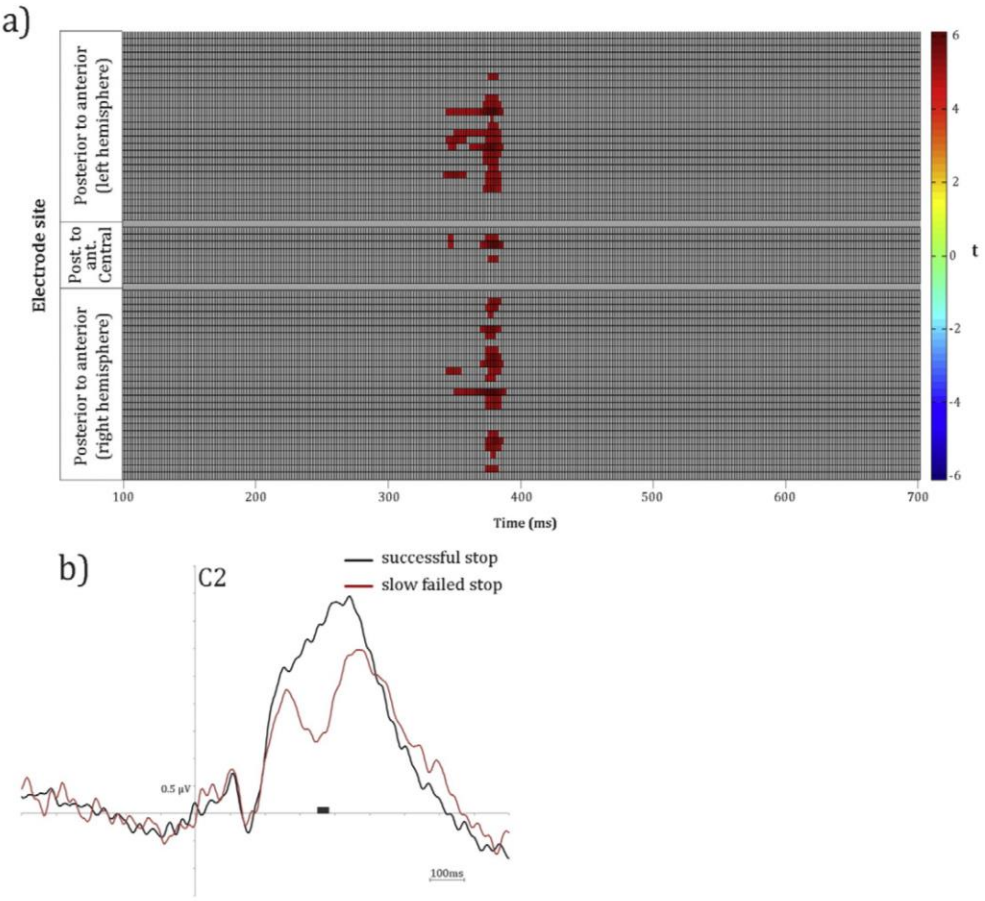

Fig. 7. Results of the mass univariate analysis. The diagram shows significant scalp ERP differences between successful stop and slow failed stop conditions in the *dependent Discriminate then Stop* (*dDtS*) strategy according to a tmax permutation test. Red and blue boxes indicate electrodes/time points in which the electrophysiological activity for the successful stop condition was greater or smaller than for the failed stop condition, respectively. Grey boxes indicate electrodes/time points in which no significant differences between conditions were found. b) Grand ERP averages at C2 electrode where differences between conditions are clearly visible. Black color bar reflects the temporal points that showed significant differences according to mass univariate analysis.

processing stages involved in selective (and also nonselective) stop signal paradigms.

SSRT for each strategy

Prior research has shown that the latency of the response interruption process (SSRT) could be correctly estimated only for the *StD* strategy, since signal discrimination is made once the response has been interrupted (Bissett and Logan, 2014). Thus, in this strategy, we calculated the SSRT over the go RT distribution, and fount that it was 268.91 ms. In the *dDtS* strategy, the violation of the independence assumption between discrimination and go processes did not allow us to estimate the SSRT based on the go RT distribution on stop trials. Currently, the best solution to overcome this problem is to use the ignore RT distribution. However, calculating SSRT with this procedure relies on some assumptions that have not yet been tested, so it should be interpreted with caution (Bissett and Logan, 2014). In our study, the mean SSRT for the *dDtS* strategy using ignore RTs was 394.22 ms. Therefore, these results indicate that SSRT was longer in the *dDtS* than in the *StD* strategy, which suggests that response interruption occurs later in the former than in the latter strategy (because in the *dDtS* strategy, signal identification occurs before the ongoing response is stopped).

Neural correlates of each strategy used to perform the task

EEG/ERP and fMRI studies using stop-signal paradigms have used at least three functional comparisons to try to isolate the neural activity associated with response inhibition: successful stop versus go, successful stop versus failed stop contrasts and the recently used successful stop versus ignore comparison. We will now discuss the differences in the neural activation patterns associated with each strategy for each of these comparisons.

Successful stop vs. slow go comparison

Results from scalp ERP recordings revealed significant differences in several temporal points and electrodes during the whole P3 temporal window. As expected, larger amplitudes in the successful stop compared to the slow go condition were observed for both strategies. However, some differences were also found depending on the strategy adopted by the participants. In this regard, while differences in the *StD* group lasted for 376 ms (starting at 208 ms after signal presentation), in the *dDtS* group differences were restricted to a narrower time window (200 ms) and showed a delayed onset (382 ms after signal presentation). Source localization analyses revealed a large amount of significant voxels in the comparison between the successful stop and the go conditions in both strategies. In the *StD* strategy, several cortical

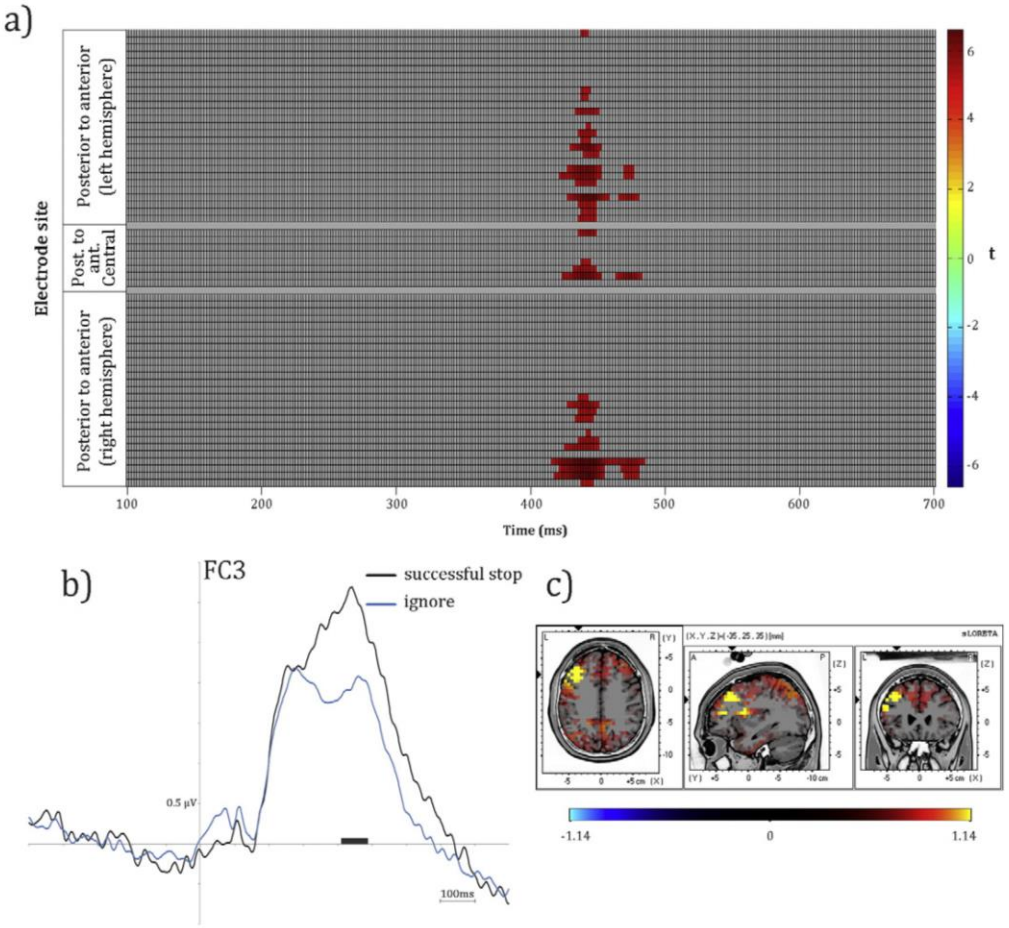

Fig. 8. a) Results of the mass univariate analysis. The diagram shows significant scalp ERP differences between successful stop and ignore conditions in the *dependent Discriminate then Stop* (*dDtS*) *strategy* according to a tmax permutation test. Red and blue boxes indicate electrodes/time points in which the electrophysiological activity for the successful stop condition was greater or smaller than for the ignore condition, respectively. Grey boxes indicate electrodes/time points in which no significant differences between conditions were found. b) Grand ERP averages at FC3 electrode where differences between conditions are clearly visible. Black color bar reflects the temporal points that showed significant differences according to mass univariate analysis. c) Source localization analysis showing increased activation during successful stop relative to go condition. Color bar represent voxels t values (log-F ratio = 1.14, $p < 0.05$).

areas including insular, parietal, prefrontal, temporal and cingulate regions showed greater activation for the successful stop than for the go condition. In the *dDts* strategy, we found more activation for the successful stop than for the go condition, mainly in parietal and frontal regions. Despite the large number of significant voxels reported for this comparison in both strategies, the number of brain areas showing activation in the *dDtS* strategy was more restricted. Nonetheless, the large number of significant temporal points, electrodes and brain regions showing significant differences between these two conditions argues in favor of the lack of specificity proposed for this functional comparison. Even though selecting the slowest go trials for each subject reduces differences in the timing of the response interruption process between successful stop and go conditions, these conditions still differ in novelty, sensory properties and in the degree to which they were learnt (unlike in the go condition, performance in the stop condition cannot be fully automatized since high accuracy can never be achieved). Thus, activation differences may reflect additional processes that occur before and/or after the interruption of the ongoing response.

Successful stop vs. slow failed stop comparison

There were very few temporal points and electrodes showing significant differences between these two conditions in both the *StD* and *dDtS* strategies. These differences were observed at the onset of the P3 (192–252 ms and 342–390 ms, respectively) and consisted of larger amplitudes for successful stop than for slow failed stop trials. Importantly, no activation differences at the voxel level were found between these conditions, either in the *StD* or in the *dDtS* strategy. These results suggest that this functional contrast is very conservative in detecting brain activity associated with response interruption. Indeed, in the *StD* strategy differences between successful stop and slow failed stop trials could be simply the consequence of differences in the beginning of the response interruption process. Although differences in the processing speed between these conditions were considerably reduced by selecting the slowest failed stop trials for each subject, the onset of ERP responses in failed stop trials is slightly delayed compared to successful stop trials. Furthermore, differences do not seem to be associated with response cancellation but with other processes since the effects at the scalp level started before the estimated SSRT in both the *StD* and *dDtS* strategies. Thus, such differences could be linked to some of the processing stages occurring before response interruption, such as response selection and/or memory retrieval (Logan et al., 2014).

To summarize, our data suggest that it is difficult to outline firm conclusions on the neural correlates of response cancellation based on either the comparisons between successful stop vs. slow go trails, and successful stop vs. slow failed stop trials. On the one hand, the highly spread activation observed over multiple temporal points and brain

regions in the successful stop versus slow go contrast, suggests that such differences do not only reflect differences in the processing stage associated with response interruption. On the other hand, differences in the successful stop versus slow failed stop contrast seem very limited. Also their timing is too early to reflect response interruption. Finally, differences between-conditions in sensorial load, relative probability, conflict monitoring or response emission are critical factors that could also account for the observed differences (Boehler et al., 2010; Li et al., 2006). Thus, a direct comparison with an ignore condition, seems appropriate to control for confounding factors and to better isolate the neural basis underlying the active cancellation of ongoing responses.

Successful stop vs. ignore comparison

The comparison between successful stop and ignore trials reached significance in few temporal points, electrodes and voxels, which suggests that ignore trials were a more accurate control condition than go trials. In this sense, ignore and stop trials had similar novelty and sensory properties, as well as similar latency ERP effects. In particular, we found greater amplitudes in the P3 time window for successful stop than for ignore trials in both strategies, although differences emerged earlier in the *StD* (330 ms) compared to the *dDtS* (416 ms) strategy. However, the onset of the electrophysiological differences between successful stop and ignore conditions emerged significantly after the mean SSRT (reliably computed over go RT distribution) in the *StD* strategy, so it is unlikely that they reflect the processing stage of response interruption. By contrast, several processes, including perceptual discrimination and decision-making, could account for such differences. In fact, participants who used the *StD* strategy would restart their response after it has been inhibited, although only in the ignore condition. To do so, they would need to discriminate stop from ignore signals and then make the decision of whether or not to respond. Although null findings should be interpreted with care, these findings may be reflecting that subjects first interrupted their response non-selectively to both ignore and stop cues and, subsequently, they restarted go processing if the signal was an ignore. Of note, the absence of differences in activation between successful stop and ignore conditions at the time by which stopping process finished (SSRT) was an expected finding for the *StD* strategy: according to behavioral evidence, subjects who use this strategy inhibit their response whenever a signal (ignore or stop) occurs (Bissett and Logan, 2014; Verbruggen & Logan, 2015).

In accordance with the finding of delayed ERP differences between the stop and the ignored conditions in the *dDtS* compared to the *StD* strategy, we observed slower SSRT in the former strategy. Indeed, the onset of neural activation differences between successful stop and ignore conditions in the *dDtS* strategy did not statistically differ from the SSRT. As we have already mentioned, the SSRT in the *dDtS* strategy was computed based on the ignore RT distribution. Since this procedure has not been validated yet, data should be interpreted with caution. Nonetheless, the presence of differences between these two conditions at the time by which stopping process finished (SSRT) provides additional support for the theoretical description of the *dDtS* strategy. In this respect, it seems that participants who adopted this strategy cancelled their ongoing responses selectively to stop but not to ignore signals. Interestingly, these differences were limited to frontocentral and parietal scalp electrodes.

In order to provide additional support to the claim that the stop versus ignore comparison in the *dDtS* but not in the *StD* strategy is particularly suitable to isolate the neural mechanisms underlying the interruption of an ongoing response, we also compared the voxel-based whole-cortex eLORETA-images that were associated to these conditions within each strategy. The results of these analyses revealed that the successful stop condition involved greater brain activation compared to the ignore condition in both strategies. In the *StD* strategy, these differences (which were observed well after SSRT, as explained) were found in occipital and posterior parietal/temporal regions. Interestingly, these areas roughly correspond to V4 and the lateral occipital cortex (LOC), which are related to object and shape recognition (Haushofer et al., 2008; Kourtzi and Kanwisher, 2000; Malach et al., 1995; Montoro et al., 2015; Vinberg and Grill-Spector, 2008). This finding would be in line with conclusions derived from scalp ERPs and behavioral data, indicating that including the ignore condition does not suffice to isolate the processes specifically associated with response interruption.

In the *dDtS* strategy, more activation in the successful stop compared to the ignore condition was found in several regions, including prefrontal, parietal and insular areas. Notably, we observed a left- rather than a right-lateralized activation. Since this is a first attempt to identify the neural signatures of response interruption for different strategies used to accomplish a selective stop-signal task, previous evidence only serves as a starting point for the interpretation of present results. In this line, although we observed activation in the pars opercularis (BA 44) and the pars triangularis (BA 45) of the IFC, which is a key region for response inhibition (Aron et al., 2014), our results suggest that response interruption would be supported by a network of several brain areas, including other frontal regions beyond IFC, as well as the insular and superior parietal cortices. Prior research has related the activation of the insula to the interruption of an ongoing response (Swick et al., 2011). Also, there is evidence suggesting that the insula participates in the detection of behaviorally salient stimuli (Cai et al., 2014) and in keeping up high levels of task performance (Boehler et al., 2010). The superior parietal cortex has been linked to the activity of the dorsal attentional network, which relates sensory to motor representations (Corbetta and Shulman, 2002; Petersen & Posner, 2012). Thus, in the *dDtS* strategy the activation of the insular and the superior parietal cortices indicates that a set of functionally heterogeneous regions is involved in the interruption of an ongoing response during a stimulus-selective stop signal task. This result is in line with those proposals that explain response inhibition in terms of the activity of a domain-general network (e.g. Hampshire, 2015). Moreover, our data agrees with prior evidence that showed the involvement of bilateral or left-lateralized cortical network in response interruption (Albert et al., 2013; Cai and Leung, 2009; Hirose et al., 2012; Leung and Cai, 2007; Li et al., 2006; Swick et al., 2008; Zhang and Li, 2012). Alternatively, it can be speculated that adding a new processing stage (signal discrimination) would induce a more serial form of processing. This serial processing would require resetting operations in working memory that recruits brain structures in the left instead of the right frontal cortices.

There is evidence indicating that learning effects modulate the activity of several brain regions during response inhibition tasks, as well as during other cognitive paradigms (Cole et al., 2010, 2013; Erika-Florence et al., 2014; Hampshire & Sharp, 2015). In selective stop-signal tasks, the stop condition leads to more errors than the ignore condition (this also happens with the go condition in traditional stop-signal tasks). As a consequence, the stop and ignore conditions would differ in their degree of learning. In this sense, in contrast to the ignore condition, the stop condition could not be fully automatized because the tracking algorithm ensures that participants fail to inhibit their response on 50% of these type of trials. Thus, even though differences in sensory, novelty and speed processing were carefully controlled for these two conditions, they likely differed in decision-making/learning processes. The next question that arises is whether the learning effects could explain the activation pattern differences between strategies. An explanation of current findings in terms of learning processes would assume that participants who used the *dDtS* strategy compared to those who used the *StD* strategy experienced more difficulties in learning how to deal with stop trials in comparison to ignore trials. As a consequence, greater activation for stop than ignore trials in the *dDtS* but not in the *StD* strategy was found. However, our results showed that differences were also evident in the *StD* strategy. Thus, an explanation of our data in terms of learning processes would also assume that learning effects modulated task performance in both strategies at a different timing. Further research is needed to understand the contribution of the learning effects on brain activity elicited during

stimulus-selective stop signal tasks, as well as their influence in the strategy adopted by participants.

Conclusions

In sum, the present results provide evidence for the neural correlates underlying behavioral strategy adoption in selective stopping tasks (Bissett and Logan, 2014). Behavioral results suggest that, even though the same task instructions were given to participants and stop and ignore trials were presented equally often, they could perform the task in at least two different ways: by inhibiting selectively to stop but not to ignore signals (*dDtS* strategy) or by inhibiting non-selectively to both signals (*StD* strategy). Remarkably, the neural effects both at scalp and source localization levels agree with those observed at a behavioral level and, importantly, with the hypotheses based on theoretical assumptions. In this sense, the neural mechanisms underlying the interruption of an ongoing response seem to be active whenever a signal (ignore or stop) appears in the *StD* strategy, given that no activation differences between successful stop and ignore trials were observed around the end of the time stopping process (SSRT reliably computed using go RT distribution). By contrast, the neural correlates of response interruption seem to be selectively involved in the *dDtS* strategy because significant activation differences were observed during successful stop and ignore trials in scalp electrodes and cortical regions which has been previously related to this process. Moreover, the onset of such differences coincides with the time at which stopping process finished in this strategy (SSRT calculated over ignore RT distribution). Further research is needed to examine the internally-driven motives that encourage participants to adopt one or another strategy. In this sense, it would also be very interesting to find a reliable procedure to determine if subjects change their strategy on a trial-by-trial basis.

The present findings also shed some light on the pursued goal of isolating the neural basis of response interruption (the final brief interactive stage of SSRT: Boucher et al., 2007). The strategy divergence observed in the current study implies that extracting conclusions from brain activation in a whole sample without further disentangling how each subject performed the selective stop-signal task would provide only a general panoramic view in which several patterns of brain activity may be operating together. Current results suggest that the best approach to isolate the neural correlates of response interruption is to compare the successful stop and ignore conditions, but importantly, only in the *dDtS* strategy. This functional comparison in this strategy revealed enhanced electrophysiological activity for successful stop compared to ignore trials that emerged before the P3 peaked. This activity was generated in the middle and inferior frontal gyri, as well as in the insula and superior parietal cortices (primarily, in the left hemisphere). The presents study highlights the importance of detecting and controlling the strategy used by participants to perform selective stopping paradigms before comparing their brain activation patterns.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2016.06.043.

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Supplementary Material 1

All participants who performed our stimulus-selective stop task had a commission error rate (failed inhibitions) of approximately 50% (all of them met the binomial stop-signal distribution criterion), providing evidence for the success of the tracking procedure. Therefore, the use of the commission error rate alone is not enough to identify subjects who did not perform the task appropriately (e.g., those with a large number of omission errors or with unusual slow go responses). In addition to these exclusion criteria, the interpretation of commission error rates in conjunction with stop-signal delay or SSD (the so-called inhibition function) can be a useful index to detect those participants who did not perform the task following task instructions (i.e., responding to go stimuli as soon as possible). If subjects carried out the task appropriately (i.e., responding as soon as possible when the go stimulus is presented, as we asked them), stopping the response should be more difficult (higher commission error rates) as SSD values increases. Therefore, a linear adjustment of error rates along SSDs should be found in each participant (if not, it is very probable that the subject was waiting to see the signal -ignore/stop- to begin the motor response). Thus, those subjects with non-linear adjustment of error rates along SSDs were probably not interrupting ongoing responses. To try to solve this problem, other researches have used a tone or visual message to advice subjects during the task that they were waiting for the stop-signal (and not pressing the key as soon as possible).

The following participants were excluded from further analysis due to non-linar adjustment of their inhibition functions (i.e., the relationship between the probability to respond during stop trials –commit an error- and SSDs): 4, 26, 33 and 33 (see Figures 1, 2, 3 and 4, respectively).

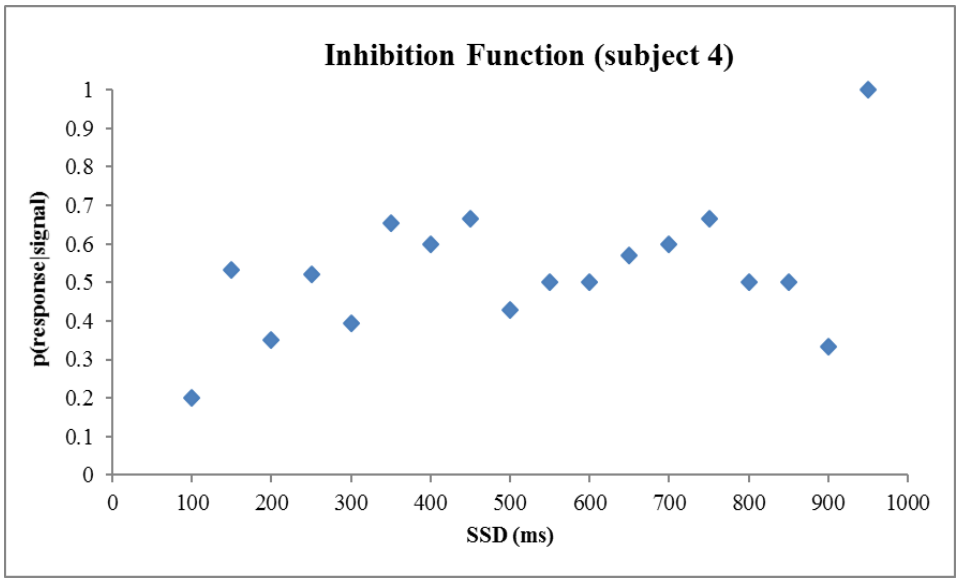

Figure S1. Inhibition function of subject 4. The relationship between the stop signal delays (SSDs) and the probability of response given the stop-signal (p(response|signal) was not linear ($F(1, 17)= 2.71$, $p=0.12$).

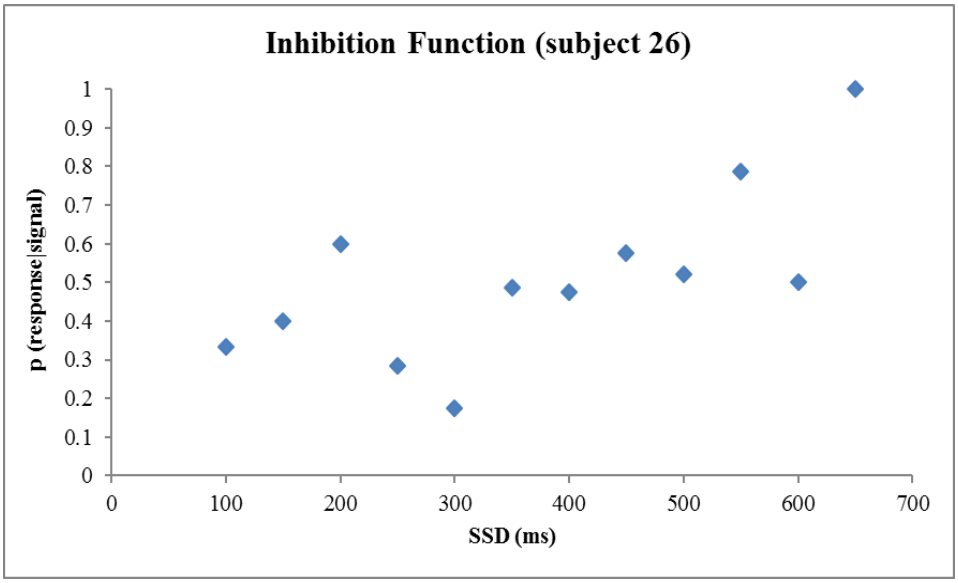

Figure S2. Inhibition function of subject **26:** The relationship between the stop signal delays (SSDs) and the probability of response given the stop-signal (p(response|signal) was not linear (F (1, 11) = 2.58, p=0.14).

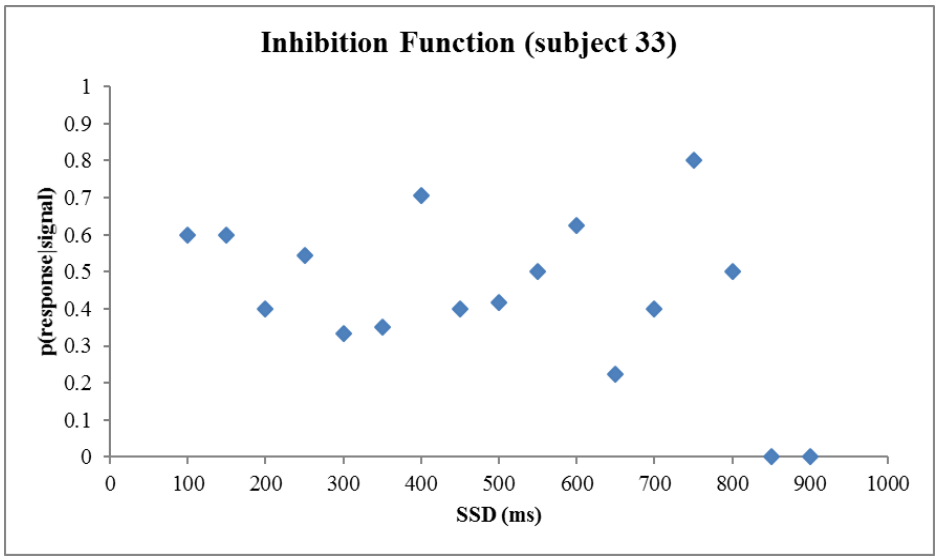

Figure S3. Inhibition function of subject 33. The relationship between the stop signal delays (SSDs) and the probability of response given the stop-signal (p(response|signal) was not linear (F (1, 15) = 1.75, p=0.2)

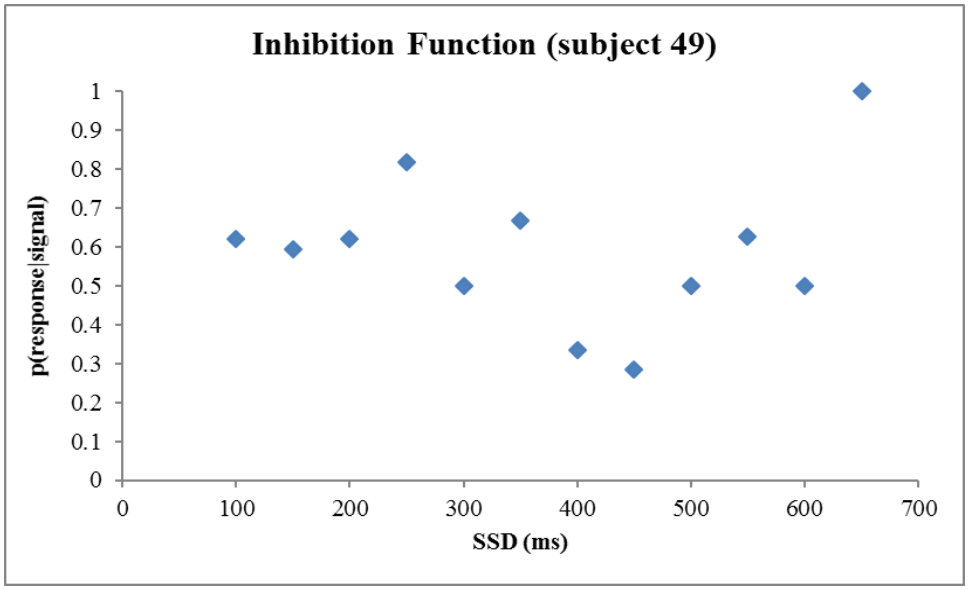

Figure S4. Inhibition function of subject 49. The relationship between the stop signal delays (SSDs) and the probability of response given the stop-signal (p(response|signal)) was not linear (F (1, 11) = 0.7, p=0.42)

Supplementary Material 2

The number of trials used in our stimulus-selective stop-signal task was determined based on a priori power analysis using G*Power 3.1 (Faul et al., 2017; 2009). Notably, to our present knowledge, the only way to determine the cognitive strategy used by each participant is to perform statistical tests between mean RTs for each condition (go vs. ignore, go vs. failed stop). Therefore, strategy identification is constricted by sample size requirements for statistical analysis (in this case, t tests). At this point it is very important to consider the great difference of sample size (i.e., number of trials) between conditions. Whereas there was a great number of go trials, ignore and stop trials only represented 20% of the total amount of trials each (150 go trials, 50 ignore trials and 50 stop trials per block). Furthermore, it should be taken into account that only failed stop trials (approximately the half of the stop trials) can be used for statistical analysis (since only in failed stop trials there is an explicit response). For this reason, we designed the experimental task taking into account the number of failed stop trials needed to make a reliable decision about whether or not RT distributions differed in each subject (in other words, to make a reliable decision about which strategy was adopted by each participant). If we compared go RTs with a small number of failed stop trials, we would probably overestimate the percentage of participants adopting the *dDtS* strategy, since it is characterized by absence of difference between these two conditions. Thus, in order to guarantee the reliability of strategy identification (controlling type I and II errors), we did an a priori power analysis. Using a type I error of $\alpha=0.05$, a power of $P=1-\beta=0.95$ and a medium size effect of 0.4, as well as an allocation ratio between both samples of 0.3 (ignore)/0.16 (failed stop), the results of this analysis estimated that at least 106 ignore, 95 failed stop and 591 go trials were required to reliably classify the strategy used by each participant. Thus, our task consisted of 1000 trials, consisting of 600 go trials, 200 ignore trials and 200 stop trials (since we predicted, according to the tracking procedure, that the probability to respond on stop trials would be around 50%).

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Supplementary Material 3

The sequence of trial presentation was randomized for each participant. Therefore, it could be possible that go trials always proceeded ignore and stop trials and some subjects became aware of this (e.g., those who used the *dDtS* strategy). These participants could have adjusted their reaction times (RTs) by not following any cognitive strategies. After examining the percentage of go trials that proceeded ignore and stop trials (see Table s3.1), this possibility seems unlikely. Table 1 shows the probability of occurrence of each trial sequence in each strategy (*StD* and *dDtS*). As can be seen, it is improbable that subjects adapted their go response on the basis of the previous trial, since the probability of go trials proceeding a stop or ignore trial is not 100% (it was approximately 60% for both the ignore-go and stop-go sequences). Notably, similar probabilities of occurrence were observed between strategies.

	Observed proportion	
Trial sequence	*Stop then Discriminate strategy*	*Dependent Discriminate then Stop strategy*
Ignore-Go	60.03%	59.47%
Ignore-Ignore	20.15%	20.53%
Ignore-Stop	19.75%	20%
Stop-Go	60.10%	61.42%
Stop-Ignore	19.83%	19.08%
Stop-Stop	20.02%	19.45%

Table s3.1. Probability of occurrence of trial sequences during the task

3.3 Conclusiones

- Los correlatos de los PER relacionados con la cancelación de una respuesta motora (P3 a nivel de superficie y distintas regiones corticales, incluido el giro frontal inferior) se observaron en la estrategia *DPd*, caracterizada por inhibir selectivamente ante la señal *stop* pero no ante la señal *ignora*r (ningún participante válido adoptó la estrategia *DPi*, también caracterizada por inhibir selectivamente). En concreto, la amplitud de P3 y la activación de diversas regiones corticales fue mayor en la condición stop-acierto que en el resto de condiciones experimentales, pero sólo en la estrategia *DPi*. Por el contrario, no se observaron diferencias en la amplitud de P3 ni en la activación de regiones corticales durante el proceso de cancelación de una respuesta en la estrategia *PD*, caracterizada por la inhibición no selectiva tanto ante la señal stop como ante la señal ignorar.

- El inicio del componente P3 (pero no N2) y el giro frontal inferior (entre otras regiones corticales) se identificaron como los correlatos de los PER más relacionados con el propio proceso de cancelación de una respuesta motora. La comparación funcional entre las condiciones stop-acierto e ignorar dentro de la estrategia de inhibición selectiva (*DPd*) se mostró como el mejor procedimiento para aislar los correlatos específicos implicados en la cancelación de una respuesta motora ya iniciada.

- La latencia estimada del tiempo medio de inhibición (*SSRT*) en la estrategia caracterizada por inhibir selectivamente (*DPd*) fue similar a la latencia de los efectos de los PER (P3) relacionados con el proceso de cancelación de la respuesta observados en el cuero cabelludo.

4 SEGUNDO EXPERIMENTO

4.1 Objetivos

- Examinar los correlatos de las principales dinámicas oscilatorias relacionadas con la cancelación de una respuesta (theta y beta), tanto a nivel de superficie como de vóxel, en cada una de las estrategias utilizadas para resolver una tarea de inhibición selectiva a nivel del estímulo.

- Identificar qué ritmo oscilatorio se relaciona específicamente con el proceso de cancelación de una respuesta motora a través del uso conjunto de una tarea de inhibición selectiva a nivel de estímulo y la comparación funcional entre las condiciones *stop-acierto* e *ignorar*.

4.2 Hipótesis

- Las dinámicas oscilatorias relacionadas con la cancelación de una respuesta motora (ritmos theta, beta-bajo y beta-alto y regiones corticales asociadas) se observará en la estrategia caracterizada por inhibir selectivamente (*DPd*) pero no en la estrategia caracterizada por inhibir no selectivamente (*PD*).

- Los ritmos beta, pero no theta, se asociarán específicamente con la cancelación de una respuesta motora, los cuales se observarán de una manera más específica en la comparación funcional entre la condición *stop-acierto* y la condición *ignorar* en las estrategias caracterizadas por inhibir selectivamente ante la señal *stop* pero no ante la señal *ignorar* (*DPi/DPd*).

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Oscillatory brain mechanisms supporting response cancellation in selective stopping strategies

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ABSTRACT

Although considerable progress has been made in understanding the neural substrates of simple or global stopping, the neural mechanisms supporting selective stopping remain less understood. The selectivity of the stop process is often required in our everyday life in situations where responses must be suppressed to certain signals but not others. Here, we examined the oscillatory brain mechanisms of response cancellation in selective stopping by controlling for the different strategies adopted by participants (n = 54) to accomplish a stimulus selective stop-signal task. We found that successfully cancelling an initiated response was specifically associated with increased oscillatory activity in the high-beta frequency range in the strategy characterized by stopping selectively (the so called *dependent Discriminate then Stop*, *dDtS*), but not in the strategy characterized by stopping non-selectively *(Stop then Discriminate, StD*). Beamforming source reconstruction suggests that this high-beta activity was mainly generated in the superior frontal gyrus (including the pre-supplementary motor area) and the middle frontal gyrus. Present findings provide neural support for the existence of different strategies for solving selective stopping tasks. Specifically, differences between strategies were observed in the oscillatory activity associated with the stop process and were restricted to the high-beta frequency range. Moreover, current results provide important evidence suggesting that high-beta oscillations in superior and middle frontal cortices play an essential role in cancelling an initiated motor response.

1. Introduction

The ability to interrupt unwanted thoughts and actions is a hallmark of goal-directed behavior. Research on the neural bases of response inhibition has mainly focused on simple or global stopping, in which all responses should be inhibited when the stop signal occurs. However, in everyday life, individuals must often inhibit certain responses but not others (response-selective stopping), or responses to certain signals but not others (stimulus-selective stopping). Here, we examined the oscillatory brain activity of stimulus selective stopping.

Prior research has shown that participants use different strategies in stimulus-selective stop signal tasks (Bissett and Logan, 2014). In this paradigm, participants are asked to respond as quickly as possible to repeated presentations of a stimulus (go trial), cancel their already initiated response when presented with a second, infrequent signal (stop trial), but continue responding if another infrequent signal is presented (continue or ignore trial). However, whereas some participants selectively interrupt their responses to stop signals (*Discriminate then Stop strategy -DtS-* strategy), other participants withhold their responses whenever a signal occurs (either ignore or stop), and thereafter restart the cancelled response if an ignore signal was presented (*Stop then Discriminate -StD*-strategy). Moreover, the *DtS* strategy can be further divided into dependent (*dDtS*) and independent (*iDtS*), depending on whether the independence assumption of the horse-race model used to

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calculate the stop-signal reaction time (SSRT) is violated or not (Bissett and Logan, 2014; Logan, 1994; Verbruggen and Logan, 2009). This model posits that response inhibition is the outcome of a race between the go and the stop process. If the go process finishes the race before the stop process, individuals will fail to inhibit their response. By contrast, if the stop process ends before the go process, the response will be inhibited. Importantly, the model assumes that go and stop processes are contextually independent (Bissett and Logan, 2014; Logan, 1994; Verbruggen and Logan, 2009). This assumption enables to predict that failed-stop responses (commission errors) should be shorter than correct go responses, given that failed-stop trials indeed reflect that going processes finished the race before stopping processes. Of note, the independence assumption between the stop and the go process is met in the *StD* strategy, but not in all individuals using the *DtS* strategy (Bisset and Logan, 2014). In those adopting the *dDtS* strategy, RTs in failed-stop trials are not shorter than RTs in correct go trials. This is thought to be due to the emergence of dependence between going and discriminating (stop vs. ignore) processes in this strategy. The violation of the independence assumption has important implications for the calculation of the SSRT (see Verbruggen and Logan, 2009). Thus, it has been recommended to use the ignore RT distribution rather than the go RT distribution to estimate the latency of the stop process (SSRT) in the *dDtS* strategy (Bisset and Logan, 2014). It is worth mentioning that this solution might be valid only under some assumptions that have not been fully tested.

To our knowledge, only two prior studies have compared the brain activity associated with each of these main strategies used in stimulus-selective stop tasks. In an event-related potentials (ERP) study using source localization methods, Sanchez-Carmona and colleagues (2016) found no differences in electrophysiological activity between stop and ignore conditions around the latency that was estimated for the stop process (i.e., the end of the SSRT) in the *StD* strategy. By contrast, differences between these two conditions were evident around the end of the SSRT for those individuals who used a strategy in which the response interruption process was selective to stop signal (*dDtS*). Specifically, they found increased P3 amplitudes and prefrontal activity for the stop versus ignore condition. These findings were in line with the behavioral-based strategy classification made by Bisset and Logan (2014), and provided new evidence suggesting that the P3 onset and its neural generators (including, inferior, medial and middle frontal gyri) may be a reliable neural marker of response cancellation process. Similarly, a recent fMRI study has also provided evidence for distinct brain activity patterns supporting selective and non-selective strategies, but differences were mainly observed in a processing stage prior to response interruption process (Sebastian et al., 2017).

The goal of the present study was to further characterize the neural mechanisms of stimulus-selective stopping strategies by examining the oscillatory neuronal activation associated with the cancellation of the ongoing response in each strategy using scalp and source-level time-frequency measures. To this end, we compared activation patterns elicited by successful stop versus successful ignore signals. This functional comparison has been recommended over traditional contrasts (successful stop vs. successful go, failed stop vs. successful stop) for isolating the neural substrates specifically underlying response cancellation, because it minimizes the influence of confounding factors such as attentional capture, conflict monitoring, and emotional frustration (Etchell et al., 2012; Li et al., 2006; Sánchez-Carmona et al., 2016; Sharp et al., 2010).

Time-frequency analysis of EEG data are expected to provide useful information beyond that coming from ERP-based analyses, because they both capture different aspects of neural activity (Cohen, 2014). For instance, a remarkable amount of information from EEG recordings might be only observed in time-frequency-based analyses if that information is non-phase-locked to stimuli (Cohen, 2014). Moreover, time-frequency data analyses allow inferences regarding neural oscillations. In this sense, it has recently been proposed that oscillatory dynamics might play a critical role in global stopping (Aron et al., 2016; Lavallee et al., 2014). Specifically, it has been argued that the global stopping-related network, which comprises prefrontal cortex (primarily, inferior frontal gyrus —IFG- and pre-supplementary motor cortex -pre--SMA- and subthalamic nucleus -STN-: (Chikazoe et al., 2007; Li et al., 2006; Li et al., 2008), might operate via communication in the beta frequency band (Aron et al., 2016; Wagner et al., 2018). Theta-band activity has also been associated with stopping (Isabella et al., 2015; Jha et al., 2015; Nigbur et al., 2011), although it is not clear yet whether activity within this band indexes the response cancellation process, or rather reflects a general marker for executive control or conflict monitoring (Cavanagh and Frank, 2014; Nigbur et al., 2011). It should be noted that many of the studies that examined the role of theta oscillations in response cancellation, also manipulated task complexity at either stimuli or response selection levels (Isabella et al., 2015; Jha et al., 2015; Wessel and Aron, 2014). This could have introduced a bias in favor of a prominent role of theta-band oscillations in response inhibition. In any case, this previous evidence mainly relies on successful stop versus failed stop comparison, while the successful stop versus ignore contrast has been little explored. Thus, the results of the present study may also shed light on the identification of the neural oscillations specifically involved in response cancellation. Additionally, although gamma-band activity has not been directly related to response cancellation, prior evidence suggests its involvement in several processes associated with stop-signal tasks such as proactive inhibition ("preparation to stop", Swan et al., 2012; Swan et al., 2013), the processing of the contextual complexity of the task (Jha et al., 2015), and the monitoring that occurs during the selection of the correct movement (Isabella et al., 2015).

The relationship between beta and theta oscillations and the different strategies used in selective stopping tasks remains unexplored. Based on prior literature (Aron et al., 2016; Wagner et al., 2018; Bisset and Logan, 2014), we hypothesize that increased beta band activity at scalp and source level will be observe during the cancellation of the ongoing response in selective (*DtS*) but not in non-selective (*StD*) stopping strategies. These findings would provide additional support for the existence of different strategies to cope with the demands involved in stimulus-selective stopping tasks (Bissett and Logan, 2014). Additionally, they would argue in favor of a critical involvement of beta oscillations in the cancelation of an initiated response. Regarding theta activity, we would expect the same pattern of results only if we assume that theta-band oscillations reflect the response cancellation process rather than executive control or conflict monitoring. Finally, given prior findings suggesting a role of gamma activity in several general aspects of stop-signal tasks, we also examined activity in this frequency band. However, since no prior study specifically associated gamma activity with response cancellation, no hypotheses could be outlined here.

2. Materials and methods

2.1. Participants

Sixty-five right-handed graduate and undergraduate students (mean age = 20.9; SD = 1.41) participated in this experiment. The study was approved by the local ethics committee, and informed consent was obtained from each subject prior to the experiment. All participants reported normal or corrected-to-normal visual acuity and had no history of neurological or psychiatric disorders. Eleven subjects were excluded from the analyses, three of them due to low overall task accuracy (more than 25 errors, <2.5 SDs below the group mean), two of them due to unusual slow go RTs (more than 970 ms, >2.5 SDs above the group mean), and four of them due to non-linear adjustment of their inhibition functions (see Sanchez-Carmona, 2016 for more details of this exclusion criterion). Briefly, if task instructions were fulfilled, the probability to respond given the stop signal (failed inhibition) should increment monotonically from 0 to 1 as stop signal delay (SSD) values increases (Verbruggen and Logan, 2009): stopping the ongoing response is easier if the stop signal is presented far in advance of the completion of the go response, and more difficult if the stop signal is presented closer to the

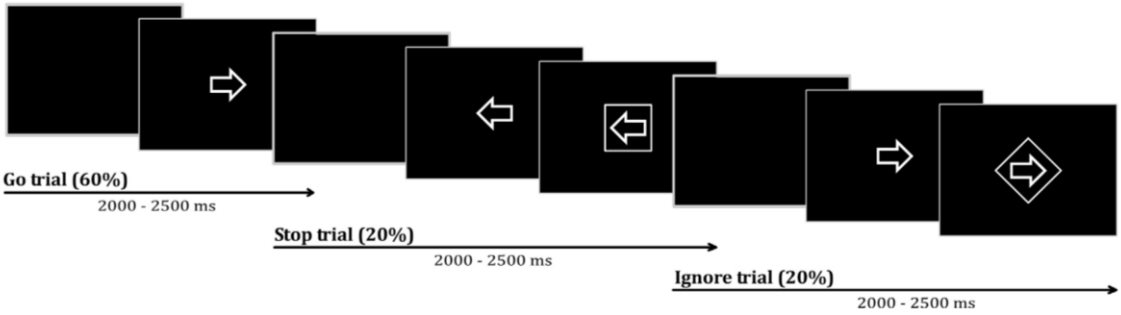

Fig. 1. Schematic representation of the stimulus-selective stop signal task.

completion of the go response. Therefore, non-linear adjustment of a subject's inhibition function indicates that the participant did not perform the task following task instructions (i.e., responding as soon as possible when the go stimulus was presented). Thus, the final sample consisted of 54 participants. All of them met the binomial stop-signal distribution criterion, reporting a 0.5 probability of stopping the ongoing response. Subsequently, participants were divided according to the strategy used to perform the experimental task. The results of the analyses indicated that 33 subjects employed the *StD* strategy, whereas 21 subjects used the *dDtS* strategy. Any subject was identified under *iDts* strategy. The resulting two groups were matched for age ($t(52) = 0.97$, $p = 0.33$) and gender ($\chi^2 = 0.56$, $p = 0.45$).

2.2. Experimental design

Participants performed a stimulus-selective stop signal task (see Sánchez-Carmona et al., 2016 for details) with three different stimuli: go, stop and ignore (Fig. 1). These stimuli were three geometrical shapes colored in white against a black background (an arrow, a square and a diamond). Subjects were instructed to press either the left or the right key arrows in a keyboard with their respective index finger whenever an arrow pointing to any of these two orientations was presented (go trial). In addition, they were informed that in some trials they had to stop their response when seeing a square surrounding the arrow (stop trial), but to continue responding if a diamond was presented around the arrow (ignore trial). Critically, we insisted participants to respond as fast and accurate as possible on go and ignore trials, and as accurate as possible on stop trials, trying to interrupt their ongoing responses. Subjects were instructed not to wait for the square or diamond to appear. Otherwise, the assumptions in which task parameter estimations were based would be compromised (Verbruggen et al., 2013). These instructions were presented to the participants on the computer monitor at the beginning of the experiment. Also, task instructions were verbally reminded to participants between blocks.

The whole task consisted of 1000 trials grouped into four blocks, each containing 250 trials (150 go, 50 stop and 50 ignore). This number of trials was based on a priori power analysis (G*Power 3.1, (Faul et al., 2009). Each trial began with a black screen with a random duration between 500 and 1000 ms. Thereafter, a go stimulus was presented. Arrows randomly pointed to the left or to the right in half of the trials. In 20% of the trials (50 trials per block), the stop signal was presented after a variable delay (SSD). This delay was initially set at 200 ms and was dynamically adjusted from stop trial to stop trial according to the individual performance of each participant. After a successful inhibition, the SSD was increased (+50 ms), which gave some advantage to the go process and reduced the probability of a successful inhibition in the next stop trial. If a response was emitted in the last stop trial, the SSD decreased (−50 ms), so the stop process started earlier and the probability of a response interruption in the next stop trial increased. This staircase algorithm was applied to achieve 0.5 probability of responding to a stop signal (Levitt, 1971). In another 20% of the trials (50 trials per block), the ignore stimulus was presented after the go stimulus. The delay was also initially fixed to 200 ms, but importantly, the ignore signal delay (ISD) was equated to the most recent SSD. Thus, the adaptive adjustment of SSD was never applied after an ignore trial. In the remaining trials (60%), only go stimuli were presented (150 trials per block).

Participants carried out the experimental task seated comfortably in an electrically shielded and sound-attenuated room. Task stimuli were presented on a computer monitor that was positioned at eye level about 65 cm in front of the participant. The stimuli were displayed on a 19-inch LCD-LED Samsung 943 N color monitor with a 75-Hz refresh rate, a 5:4 aspect ratio, and a resolution of 1024 × 768. Before the beginning of the experimental blocks, subjects completed a practice block of 100 trials to ensure that they understood task instructions (60 go, 20 stop and 20 ignore trials; initial SSD = 200 ms). The task was designed and implemented in MATLAB, using Psychtoolbox (www.psychtoolbox.org). The Matlab script of stop-it (Verbruggen et al., 2008) served as starting point for programming our stimulus-selective stop-signal task.

2.3. EEG recording

Electroencephalogram (EEG) activity was recorded from 62 electrode locations mounted in an electrode cap (BrainVision), arranged according to the International 10–10 system (American Electroencephalographic Society, 1991). All electrodes were referenced to the average of mastoids. Bipolar horizontal and vertical electrooculograms (EOGs) were also recorded to monitor eye movements and blinks. Electrode impedances were kept below 10 kΩ. Recordings were amplified using BrainAmp amplifiers (BrainProducts, Munich, Germany), continuously digitized at a sample rate of 1000 Hz, and filtered online with a frequency band-pass of 0.01–100 Hz.

2.4. Data analysis

2.4.1. Behavioral analysis

Each subject's strategy was determined by comparing their mean no-signal (go) RT, stop-respond RT (incorrectly executed responses on stop-signal trials) and ignore RT (correctly executed response on ignore-signal trials), following the procedure described by Bisset and Logan (2014). Participants were categorically [1]classified as using the *iDtS* strategy (stop-respond RT<no-signal RT ≮ignore RT), *StD* strategy (stop-respond RT<no-signal RT<ignore RT) or *dDtS* strategy (stop-respond RT≮no--signal RT<ignore RT). Bayes Factor was used to compare the evidence

[1] Participants were also dimensionally classified in a 2D space using go and failed stop reaction times (RT) in order to examine whether the individual difference on the *StD-DtS* dimension correlate with neural oscillatory features. A detailed description of this dimensional approach to selective stopping strategies and the correlational analysis with oscillatory measures can be found in the Supplementary Material.

for and against the null hypotheses without bias (Rouder et al., 2009). The Bayes factor is a ratio that contrasts the likelihood of the data fitting under the null hypothesis with the likelihood of fitting under the alternative hypothesis. A Bayes factor of 1 means that the odds in favor of the null hypothesis are no better than the odds against it. Bayes factor was computed by calculating the mean and standard deviations of no-signal, stop-respond, and ignore RTs separately for each subject. Subsequently, we calculated two independent samples t tests comparing stop-respond RT with no-signal RT and ignore RT with no-signal RT, respectively. Rouder's Bayes factor calculator on the Perception and Cognition Lab website (http://pcl.missouri.edu/bf-two-sample) was used to convert t tests and sample sizes to Bayes factors. The recommended Jeffrey-Zellner-Slow Prior with the default value of 1 was used, which is appropriate if there are no strong prior assumptions (Rouder et al., 2009). SSRTs were computed via the integration method since it has been shown to be less biased than the traditional mean method when the normality criterion in the go RT distribution is violated (Verbruggen et al., 2013). We computed SSRTs over both go and ignore RT distributions, as recommended by Bisset and Logan (2014) when dealing with these strategies. Notably, the independence assumption made by the horse race model is violated in the dDtS strategy, so calculating SSRT using the go RT distribution as the underlying go distribution on stop trials is an invalid method. As Bisset and Logan (2014) have suggested, a possible solution to this problem is to use the ignore RT distribution to calculate SSRT in this strategy. However, it is worth mentioning that this procedure might be valid only under some assumptions that have not been yet tested. Therefore, SSRTs computed using the ignore RT distribution for the subjects who adopted the dDtS strategy should be interpreted with caution until being validated.

2.4.2. Preprocesing and time-frequency analysis

Data were analyzed using Fieldtrip package (http://www.fieldtriptoolbox.org (Oostenveld et al., 2011); for MATLAB (Mathworks, Inc.). EEG activity was first down-sampled to 500 Hz to save calculation time and memory costs. The continuous EEG was then segmented into epochs time-locked to stop/ignore signal onset. The duration of the epochs was 1900 ms (from −700 to +1200 ms). However, to overcome problems arising from the choice of the baseline period just prior to stop/ignore onset (some epochs but not others may contain activity related to go processing), we rather employed the time interval between 400 and 200 ms before go stimulus onset as baseline (during this period, participants saw a black screen -inter-trial interval-). Analyses were focused on stop and ignore trials to maximize the control of confounding variables that are not related to response cancellation (Albert et al., 2013; Etchell et al., 2012; Sánchez-Carmona et al., 2016; Sharp et al., 2010). Importantly, ignore trials in which subjects did not press any key or pressed a wrong key to the keyboard, as well as stop trials in which subjects responded to stop stimulus were discarded. Likewise, we also discarded stop and ignore trials where a response was emitted before signal presentation. Independent component analysis (ICA) was then used to remove ocular and other artifacts from individual EEG data sets (Jung et al., 2000). After the ICA-based removing process, visual inspection of individual EEG epochs was also conducted to remove residual artifacts. The artifact rejection and exclusion of incorrect or miss trials, led to the average admission of 148.9 (18.89) ignore trials and 77.8 (10.03) stop trials.

To obtain a time-frequency representation of each single trial, we applied the short-time Fast Fourier Transform (FFT) with a Hanning tapper. The FFT was performed on overlapping 400-ms windows in 950 steps. Such length was selected to capture at least one cycle of the minimum frequency aimed to study (i.e., theta band activity). Given the frequency resolution provided by the selected time segment and the sampling rate used, we selected the closest frequency bin to a frequency comprised between 2.5 and 50 Hz in a logarithmic scale. Thus, the resulting power at each time point and frequency bin was consecutively placed into a time-frequency space for each trial and participant, from −500 to +1000 after stop/ignore stimulus. Before statistical analyses, the resulted power was normalized by taking a decibel transformation relative to baseline ($dB_{tf} = 10\log10[activity_{tf}$ - mean $(baseline_f)]$).

2.4.3. Statistical analysis at scalp level

We focused on theta (4–7 Hz), beta (12–30 Hz) and gamma (31–50 Hz) bands oscillations because they have been proposed to play important roles in stopping (Aron et al., 2016; Huster et al., 2013; Isabella et al., 2015; Jha et al., 2015; Swann et al., 2009; Swann et al., 2012). Following previous studies (Lavallee et al., 2014; Marco-Pallarés et al., 2008; Ritter et al., 2009; Swann et al., 2009; Wagner et al., 2018), beta band was divided into lower (12–20 Hz) and upper subbands (21–30 Hz). Therefore, mean theta (4–7 Hz), low-beta (12–20 Hz), high-beta (21–30 Hz) and gamma (31–50 Hz) values were extracted between 100 ms and 700 ms post-stop and ignore stimulus, thus comprising enough time to include SSRT latency. Importantly, due to the logarithmic scale employed in the time-frequency analysis, each average included an equivalent number of frequency bins, thus avoiding the over-representation of higher frequencies. So that, taking advantage of the high temporal resolution of EEG, we aimed to fully explore when and where power changes are induced by each signal type (stop and ignore) with minimal a priori assumption.

To handle the multiple comparison problem, we performed cluster-based nonparametric permutation tests. Under the null hypothesis of exchangeability, marginal distributions of stop and ignore conditions are equal, so relative power observed in them can be shuffled. Thus, time-channel samples were highlighted as significant if their value exceeds the 97.5th percentile or do not surpass the 2.5th percentile (statistical threshold at $p = 0.05$ for a two-sided test) of an empirical null hypothesis distribution computed in the following way: in every shuffle, a paired two-sided *t*-test was performed between each time-channel sample, setting up the pre-cluster threshold at $p < 0.05$. However, given the autocorrelation in the data, a finding was considered significant only if enough neighbouring samples were also significant (spatio-temporal contiguity criterion). After each iteration, statistical maps of suprathreshold and infrathreshold clusters were conformed, and only the largest and the smallest sum of test statistics within them were stored, controlling the multiple comparison problem. This procedure was repeated 1000 times to build a distribution of the largest suprathreshold and the smallest infrathreshold clusters that can be expected under the null hypothesis. All permutation statistics were done using FieldTrip.

2.4.4. Source reconstruction

To estimate the neural sources underlying the experimental effects observed at scalp level, a time domain linearly constrained minimum variance (LCMV) beamformer approach was used (Gross et al., 2001; Van Veen, Van Drongelen, Yuchtman and Suzuki, 1997), as implemented in Fieldtrip. Specifically, this source reconstruction method scans every brain location testing for the likelihood of activity being on each of them, based on the assumption that the time course at a given location is uncorrelated with all other different sources. Importantly, the beamformer approach has several advantages over the dipole modeling procedure, including no a priori assumptions about the amount or the location of the underling sources. Thus, it implements an optimized spatial filter that unifies two constraints: the maximization of the activity at the location of interest and the suppression of all other interfering activity out of interest (i.e., noise and other sources). The procedure followed two steps: forward and inverse model computation. First, to ensure maximal specificity, a forward model derived from a standardized realistic head model was computed, defining how each source is visible at the scalp level. To this end, the volume conductor was discretized in a regular 3-D grid of 12 mm and the leadfield matrix was computed for each voxel. Then, a common spatial filter between stop and ignore conditions was designed. To this end, time segments of both experimental conditions were concatenated and re-referenced to the common average. Then the covariance matrix was calculated to determine the spatial filter coefficients. Thus, the source strength at each grid point was estimated by multiplying data for

each experimental condition by this common filter. Based on the results of the statistical comparison between the time-frequency decompositions of stop and ignore trials at scalp level, data was bandpass filtered in the frequency range of interest. Then, the absolute value of its Hilbert transform was computed from −200 to +700 ms respect the go stimulus, separately for each experimental condition and individual subject. Once we identified which frequency band was sensitive to the experimental manipulation at the surface level, frequency resolution was no longer relevant for beamforming source reconstruction. Thus, we used the continuous Hilbert transform, rather than the short-time FFT, to better capture the time course of the effects. Before submitting source estimations to statistical analysis, a baseline transform was performed to control against the power bias towards the center of the head. Concretely, for each subject and experimental condition, absolute power changes with respect to baseline was calculated at each source grid location [(post-stimulus power − pre-stimulus power)].

2.4.5. Statistical analysis at source level

Cortical power volumes for the stop and ignore conditions were then submitted to statistical analysis. Oscillatory power projected into cortical source space for stop and ignore conditions was compared using the same nonparametric cluster-based permutation statistics as described for the time frequency scalp level data. However, as the beamformer solutions (3-dimensional dipole grids in MNI space) already reflect power changes

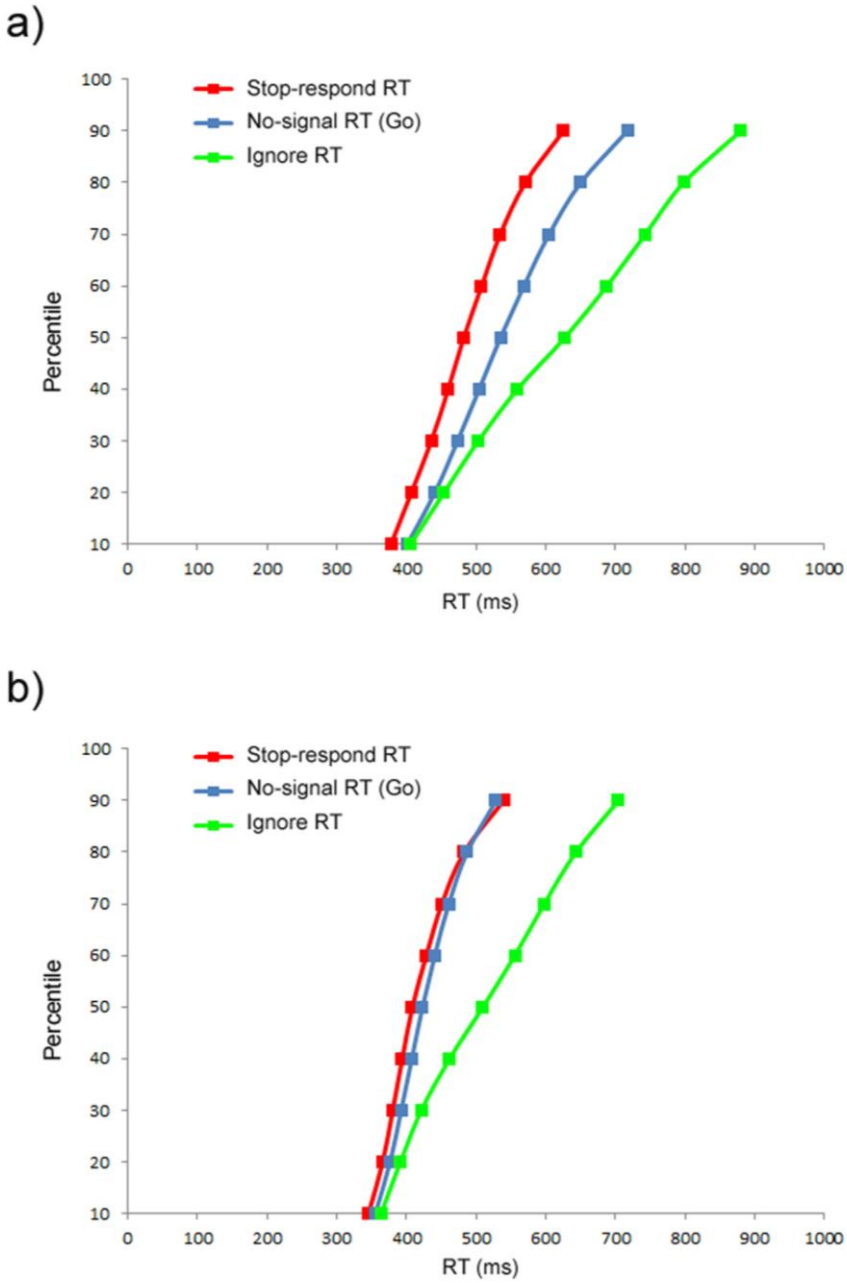

Fig. 2. Quantile averages of RT for stop-respond trials, no-signal (Go) trials, and ignore trials for participants who adopted the *Stop then Discriminate* (*StD*) strategy (a), and subjects who adopted the dependent *Discriminate then Stop* (*dDtS*) strategy (b).

within a certain time-frequency window, clusters were formed along the spatial dimension only.

3. Results

3.1. Behavioral results

As explained before, the strategy followed by each participant was estimated by comparing their mean no-signal (go) RT, stop-respond RT and ignore RT. The result of these analyses indicated that none of the subjects adopted an *iDtS* strategy to perform the task. Evidence for the use of the *StD* strategy was found in 33 out of the 54 subjects. Therefore, the remaining 21 subjects used a *dDtS* strategy. Repeated measures t-tests performed at group level corroborated this individual distinction. In the *StD* group, mean stop-respond RT were faster than mean no-signal RT ($t(32) = -8.591$, $p < 0.001$, Cohen's $d = 1.78$), and mean ignore RT were slower than mean no-signal RT ($t(32) = -14.259$, $p < 0.001$, Cohen's $d = -2.21$). The group that adopted a *dDtS* strategy showed mean stop-respond RT no significantly slower than mean no-signal RT ($t(20) = -0.602$, $p = 0.554$), and mean ignore RTs slower than mean no-signal RTs ($t(20) = -27.676$, $p < 0.001$, Cohen's $d = -4.253$). Their cumulative distributions are represented in Fig. 2. Means and standard deviations RTs across strategies are shown in Table 1.

SSRTs over both go and ignore distributions were computed for each strategy using the integration method (means and SD are shown in Table 1), knowing that this computation was only strictly valid for the *StD* strategy (Bissett and Logan, 2014).

3.2. Time-frequency results

3.2.1. Stop then discriminate (StD) strategy

Fig. 3a shows the grand-averaged time-frequency plot for each condition in a representative electrode. Significant clusters were observed above the significant threshold. However, differences were highly patent in the opposite direction, with higher power for ignore relative to successful stop condition (Fig. 3c). Specifically, differences were observed between spectral changes induced by successful ignore relative to successful stop condition in theta and low-beta bands ($ps < 0.001$). Regarding the former, the time course of statistical significance revealed that the effect only started after SSRT ending (after 380 ms), and was visible in the whole scalp (Fig. 3c and Supplementary Figure 1a). Regarding the latter, ignore low-beta power started to be significantly more positive than stop related activity at 130 ms. and lasted until the end of the trial; however, differences were interrupted between 240 and 400 ms after signal presentation (just at the time of the SSRT and the ignore RT latency) in almost all electrode positions (Fig. 3c and Supplementary Figure 1b). No differences were observed either in the high-beta (negative-cluster, $p = 0.27$) or the gamma bands (negative-cluster, $p = 0.13$). Given its latency, none of the differences observed at scalp level could be related to response cancellation process. Therefore, source reconstruction was not performed in this group of subjects.

Table 1
Sample characteristics and task performance of study participants (means and standard deviations).

	dDtS	StD
N	21	33
Age	21.14 (1.45)	20.75 (1.39)
No-signal	436.58 (25.19)	547.09 (44.68)
Stop	433.87 (20.86)	488.95 (10.98)
Ignore	523.01 (13.81)	625.30 (22.12)
SSRT go	291.31 (57.54)	246.83(57.34)
SSRT ignore	378.84 (51.05)	307.24 (69.60)
Mean SSD	169.93 (30.92)	308.33(80.24)

Abbreviations: dDtS, dependent Discriminate then Stop strategy; StD, Stop then Discriminate strategy; RT, reaction times; SSRT, stop signal reaction times; SSRTgo, SSRT computed on the go distribution using the integration method; SSRTignore, SSRT computed on the ignore distribution using the integration method. Mean SSD, mean stop signal delay.

3.2.2. Dependent Discriminate then stop (dDtS) strategy

Fig. 3b shows the grand-averaged time-frequency plot for each condition in a representative electrode. When this strategy was used, the stop processing induced significant increased high beta band activity relative to the ignore condition from 260 to 514 ms after the stop stimulus onset (cluster-based permutation test, $p = 0.021$; Figs. 3d and 4). Differences started at left frontal electrodes and then expanded to almost all frontal and fronto-central locations (Fig. 4ab). Notably, the estimated latency of the end of the stop process (i.e., the SSRT) matched the timing of the differences observed in the high beta-band between stop and ignore conditions in this strategy (see vertical lines on x-axes in Fig. 3d). No significant differences were observed in the theta (negative-cluster, $p = 0.16$) or in the gamma bands (negative-cluster, $p = 0.12$).

To reconstruct the neural generators underlying high beta activation differences between stop and ignore conditions, a beamforming analysis was performed at 21–30 Hz frequency range in a 50 ms time window around the estimated SSRT. Fig. 4b shows significant clusters ($p < 0.05$) arising from a cluster-based permutation test (Maris and Oostenveld, 2007). The main generator of these differences (stop>ignore) was located in the anterior portion of the medial superior frontal cortex (pre-supplementary motor area, preSMA; BAs 8; MNI coordinates $X = -18$, $Y = 29$, $Z = 38$; see Fig. 5), extending to dorsolateral prefrontal regions (BA 9) and medially to anterior cingulate cortex (BA 32 and BA 24).

3.2.3. Ad hoc between-strategy analysis

The results of within-strategy analyses, both at the surface and voxel level, suggested that high-beta oscillations are critically involved in selective response cancellation. However, beta-band oscillations have also been implicated in motor response execution (Engel and Fries, 2010; Kilavik et al., 2013). Thus, in order to provide further support for the role of high-beta oscillations in selective response cancellation, we compared the ignore condition of the *dDtS* with the ignore condition of the *StD* strategy. We chose this comparison because ignore trials in the *StD* involve first response cancellation followed by response execution, whereas only response execution is need for ignore trials in the *dDtS* (in this strategy, individuals do not inhibit their responses in the ignore condition: (Bissett and Logan, 2014). Therefore, the results from this between-strategy analysis, might be particularly relevant to establish the role of high-beta activity in response cancellation. In particular, we expected higher high-beta activity for ignore *StD* than for *dDtS* ignore trials.

A cluster-based nonparametric permutation analysis was performed to compare ignore conditions between strategies using the same procedure as in the within-strategy analyses. We conducted one sided-test analyses in those time-channel samples showing higher high-beta power for *StD* ignore trials compared to *dDtS* ignore trials. The results revealed higher high-beta activity in *StD* ignore trials than in *dDtS* ignore trials (cluster-based permutation test, $p = 0.04$; Supplementary Figure 2). This increased activity emerged around the latency that has been estimated for the stop process in the *StD* (i.e., the SSRT: the time when the motor response is thought to be cancelled in this strategy). However, unlike the effect found in the successful stop versus ignore comparison within the *dDtS* strategy, the effect remained for several hundred milliseconds. This finding suggests that our between-strategy contrast involves additional processes beyond response cancellation. Therefore, although the results from the comparison between ignore trials in both strategies support the role of high beta band in response cancelation, some caution is needed when interpreting this ad hoc and little examined comparison.

4. Discussion

We investigated for the first time the oscillatory neuronal mechanisms supporting response cancellation for the two main strategies used

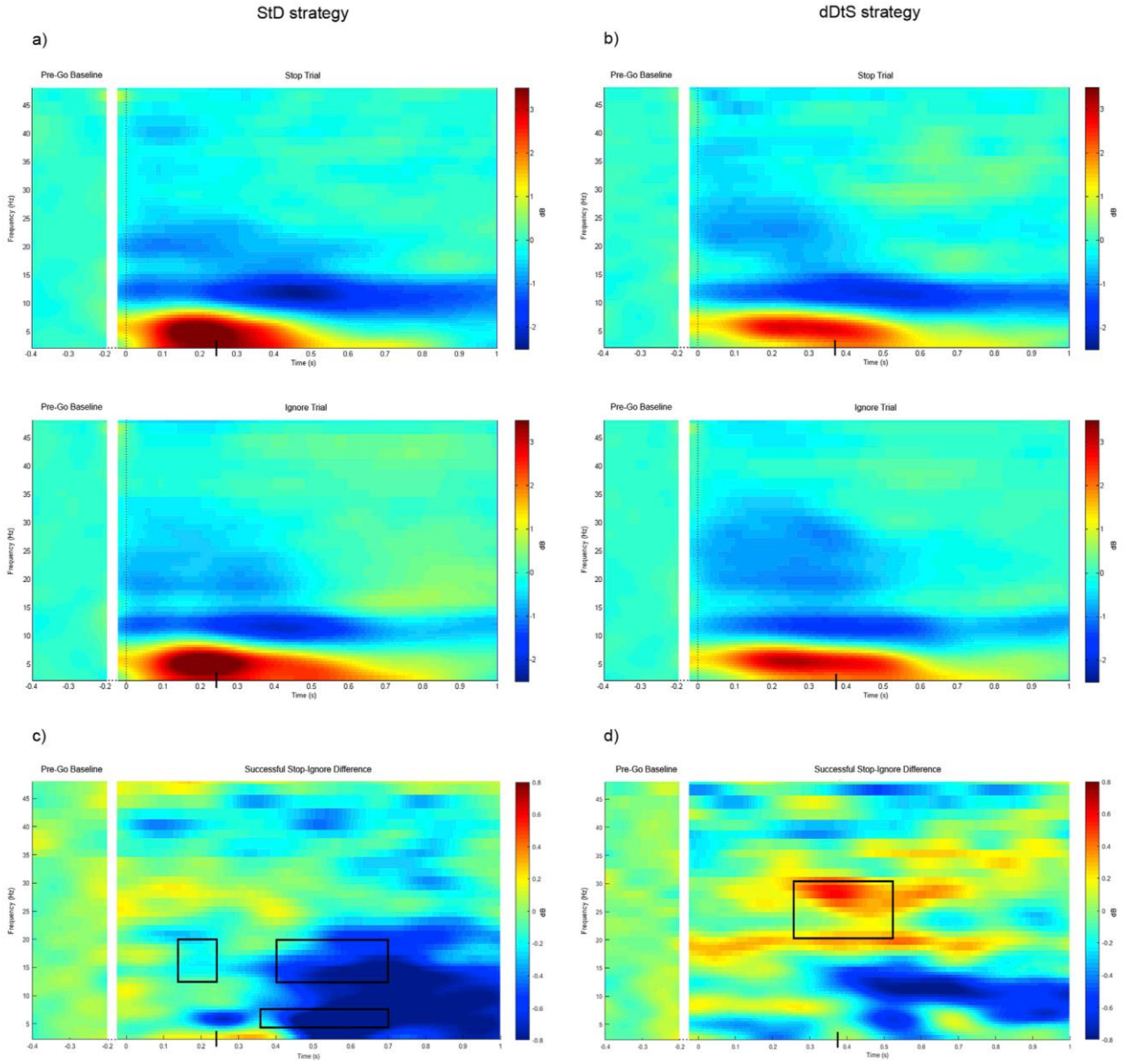

Fig. 3. Time-frequency plots for the successful stop and successful ignore conditions in the *Stop then Discriminate* (*StD*) strategy (a) and *dependent Discriminate then Stop* (dDtS) strategy (b) for 2.5–50 Hz at a representative electrode location (FC3). To avoid artifact contamination, a −400 to −200 baseline prior go stimulus onset was used. Thus, x-axis was broken in two sections, to show both pre-go baseline and signal-related power. Total power is expressed as decibel transformation relative to baseline. The dotted vertical line indicates the signal onset (ignore or stop). Time-frequency plot for the power difference between successful stop and successful ignore trials in the *StD* (c) and *dDts* (d) strategy. Relative power was averaged over the significant electrodes observed in statistical analyses. The black box highlights both the frequencies and the time ranges in which significant results were observed. in each strategy. The black vertical line on the x-axis represents the mean stop signal reaction time (SSRT) for each strategy.

in stimulus-selective stopping paradigms. Recent proposals have claimed that brain oscillations may play a central role in stopping, at least in a broad sense. Specifically, it has been argued that the frontosubthalamic circuit supporting global stopping might operate via communication trough the beta frequency band (Aron et al., 2016). Although this proposal still needs further support, some evidence from electrophysiological studies points to a role of spectral changes in the beta band frequency range in response cancellation (Lavallee et al., 2014; Pastötter et al., 2008; N. Swann et al., 2009; Wagner et al., 2018). However, the mechanisms behind these effects remain to be clarified. Additionally, theta-band frequency oscillations have also been associated with stopping initiated responses (Isabella et al., 2015; Jha et al., 2015; Nigbur et al., 2011), although it is still under debate whether theta-band effects are directly involved in response cancellation or rather reflect a general marker of executive control or conflict monitoring (Nigbur et al., 2011). As we will elaborate later, here we provide support for the view that oscillatory activity in the high beta frequency range, but not in the theta band, is specifically associated with response cancellation.

Following the criteria proposed by Bisset and Logan (2014), we first identified the strategy adopted by each participant to perform the stimulus-selective stop-signal task. Most of them used the *StD* strategy (61%), which is characterized by stopping non-selectively to both ignore

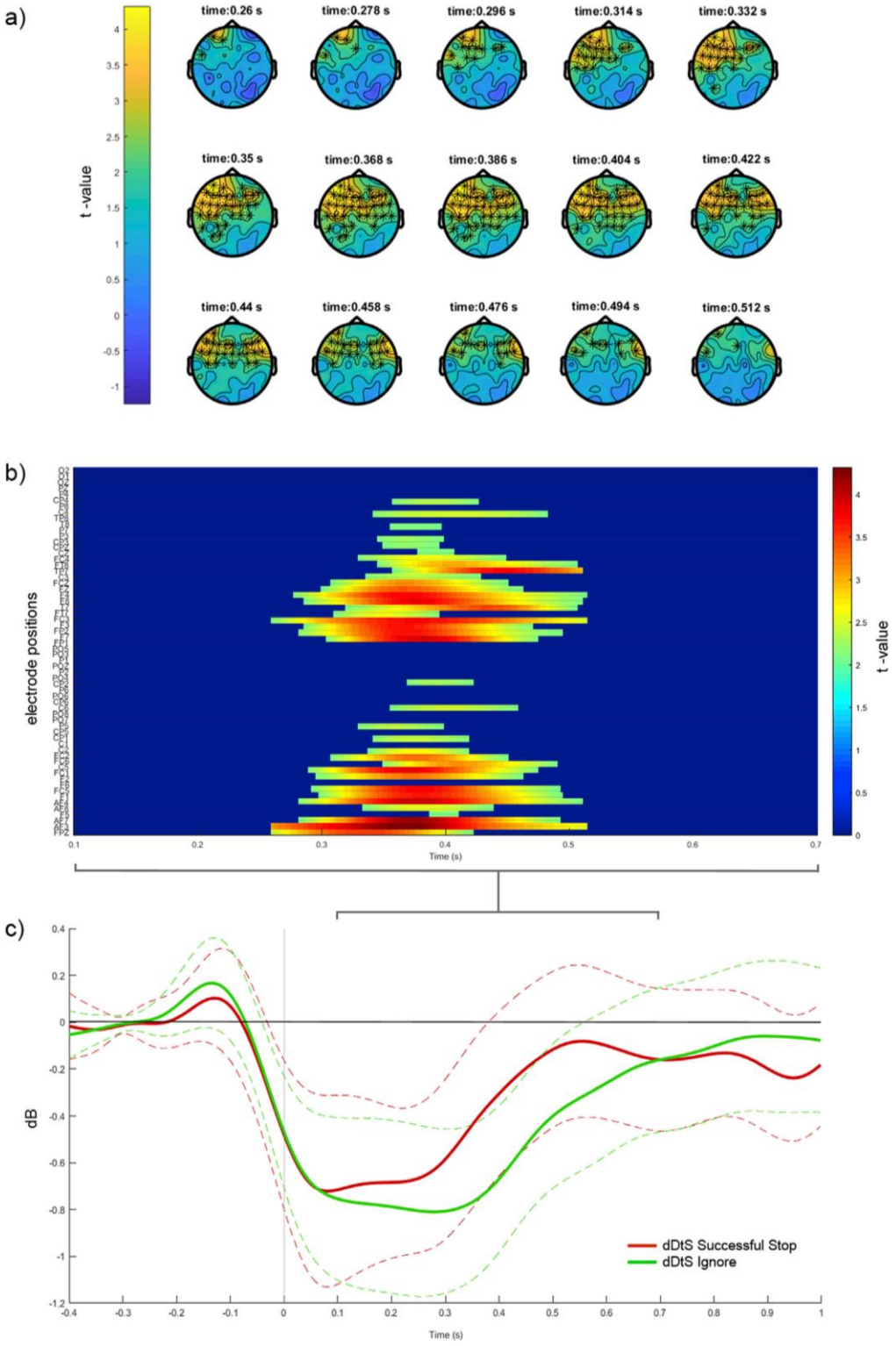

Fig. 4. a) Topographic distribution along the time course of the significant cluster observed in the high-beta frequency band (21–30 Hz) between successful stop and successful ignore trials in the *dependent Discriminate then Stop* (*dDtS)* strategy. Significant electrodes ($p < 0.02$) are highlighted with a black star. Color bar represents t values. b) Positive significant clusters of non-parametrical permutation analysis in the high-beta frequency band showing greater power for successful stop compared to successful ignore condition in the *dDtS* strategy. Color bar represents t values. c) Time course of total high-beta power, averaged for significant electrodes, comparing successful stop and successful ignore trials in the *dDtS* strategy. Dashed lines represent 95% confidence interval.

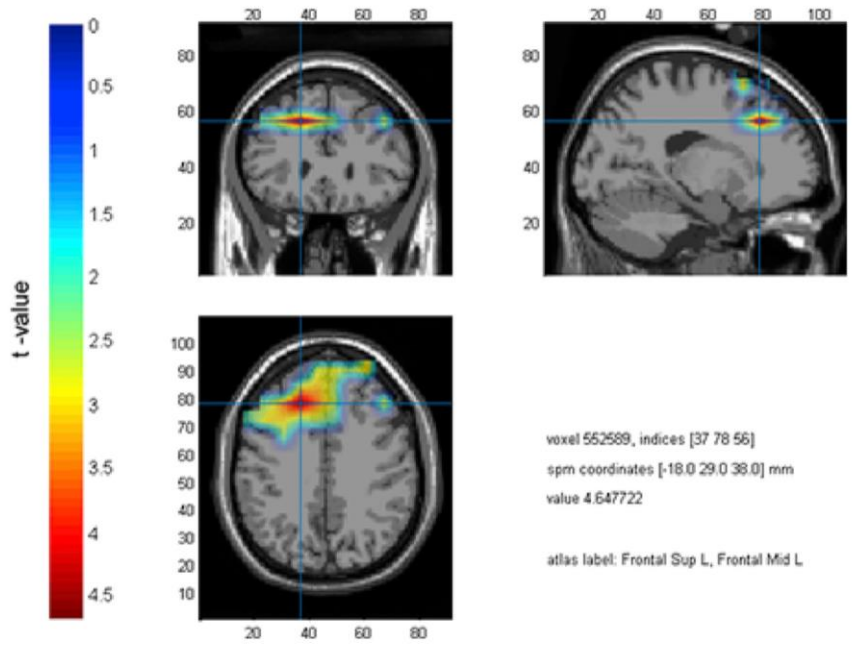

Fig. 5. Beamforming reconstruction of the neural sources of high-beta band activity observed at the scalp level in the *dependent Discriminate then Stop (dDtS)* strategy (successful stop > successful ignore). Color bar represents t values.

and stop signals. The remaining participants (39%) used the *dDtS* strategy in which the ongoing response is selectively interrupted when the stop signal is presented. These percentages are similar to those observed in our previous study (Sánchez-Carmona et al., 2016), but differ from those reported by Bisset and Logan (2014) and by Sebastian et al., (2017). One possible explanation for this discrepancy is that these two studies used color as the feature to discriminate between stop and ignore stimuli. By contrast, as in our prior study, we used here perceptually similar geometric, black-colored shapes that only differed in orientation. Therefore, the perceptual similarity between stop and ignore signals in our task might have biased participants to adopt a more conservative strategy (i.e., *StD*). Indeed, the results from a recent behavioral experiment supported this notion by showing that the degree of perceptual similarity of ignore and stop signals bias strategy adoption processes (Sánchez-Carmona et al., in preparation).

Subsequently, we examined oscillatory activation associated with response cancellation for each strategy. We compared successful stop versus successful ignore conditions, a comparison that has been recommended to identify the neural correlates specifically linked to response cancellation (Etchell et al., 2012; Sánchez-Carmona et al., 2016; Sharp et al., 2010). This functional comparison seems to overcome some of the limitations of traditional contrasts (e.g., successful stop vs. go, successful stop vs. failed stop) by minimizing the influence of confounding factors such as novelty, emotional and/or perceptive/sensory effects.

When comparing activity elicited by the successful stop and the ignore conditions in the selective stopping strategy (*dDtS*), we found increased power in the higher beta band. This effect seems to be related to a smaller high-beta band desynchronization for the stop relative to the ignore condition, which is in line with the results from several previous studies with non-selective stop signal and go/no go tasks that found reduced beta band desynchronization in response to stop/nogo trials (Kühn et al., 2004; Nigbur et al., 2011). It has been proposed that beta event-related desynchronization would represent active stopping mediated by a cortical inhibition, whereas beta event-related synchronization would reflect a decrease of cortical activation in a more passive way (Pastötter et al., 2008). Notably, the increased activity in the high-beta frequency band during response cancellation in the *dDtS* strategy was more evident at frontal scalp electrodes and emerged just before the latency of the response cancellation process as measured by the SSRT computed over the ignore distribution (Bissett and Logan, 2014). Therefore, these results suggest that oscillatory activity in the high-beta frequency range is critically involved in response cancellation, extending the findings from a prior ERP investigation that observed differences between successful stop and successful ignore conditions at the onset of the P3 only in this strategy (Sánchez-Carmona et al., 2016).

The comparison between successful stop and ignore conditions in the *dDtS* strategy was significant for the beta, but not for the theta band. Thus, we failed to provide evidence for the hypothesis that theta-band oscillatory activity specifically reflects the processing stage of response cancellation. Rather, it might represent a more general marker of executive control, since we observed an increased theta-band activation for both stop and ignore relative to go stimulus (data not shown). This idea would be in line with some prior findings (Aron et al., 2016; Cavanagh and Frank, 2014; Nigbur et al., 2011). In a similar vein, no significant differences were observed in gamma activity, which suggests that this band is not specifically involved in selective response cancellation.

In the non-selective stopping strategy (*StD*), no stopping-related differences between successful stop and ignore conditions were observed in the high beta frequency band. Although null findings should be interpreted with caution, these results would suggest that both conditions induced equivalent spectral changes. Nonetheless, the absence of oscillatory activity differences between successful stop and ignore conditions at the time by which stopping process ended (SSRT) was an expected finding for the *StD* strategy. Indeed, prior behavioral data have shown that individuals who use this strategy stop their responses whenever a signal occurs without further discriminating between stop and ignore trials (Bisset and Logan, 2014). It has been suggested that spectral changes that are not specifically linked to response cancellation might underlay differences between the stop and ignore conditions within this strategy (Sebastian et al., 2017). In accordance with this view, in the current experiment we observed differences in the *StD* strategy between successful stop and ignore trials in both the theta and low-beta bands. However, these differences were not in the expected direction since we found higher activity for ignore than for stop trials (reduced

event-related desynchronization). It is worthy to mention that the latency of these effects makes it unlikely that they reflect response cancellation. On the one hand, differences in the theta band only started after SSRT ending, which could be associated with the higher conflict induced by the requirement of restarting a response for ignore condition in this strategy. On the other hand, differences in the low-beta frequency band were vanished in the time range of both RTs and SSRT for ignored trials computed over the go distribution. It could be argued that this finding would reflect response cancellation in both conditions. However, to establish a reliable link between low-beta activity and response cancellation, similar modulations in this frequency band should have also been also observed in the *dDtS* strategy. Since we did not found such differences, we concluded that low beta oscillations do not seem to be related to selective stopping.

Regarding the neural origin of these effects, we found that the main cortical generator underlying differences in the high beta band between stop and ignore conditions in the *dDtS* strategy were mainly located in the medial superior frontal cortex, including the preSMA. This region, in conjunction with the IFC, is thought to play a key role in global stopping by implementing inhibitory control via direct inputs to the STN (the so-called *hyperdirect pathway*). Although the contribution of this brain area to selective stopping remains poorly understood, it has been hypothesized that reactive selective stopping may implemented via the so-called *indirect pathway* (Aron, 2011). Again, the preSMA (and/or the IFC) would be a critical region within this pathway that would involve the additional activation of the caudate and the external globus pallidus (see Fig. 5 of Aron, 2011). Here, we provide further evidence for this hypothesis by showing a critical involvement of the preSMA in response cancellation during selective stopping. Additionally, we found activation of the dorsolateral prefrontal cortex (dlPFC) during response cancellation in the *dDtS* strategy. Although the dlPFC is not typically activated in global stopping tasks, some authors have suggested that this region could be involved in other complex forms of inhibition (including proactive and selective stopping), in which working memory and decision-making demands increase (Aron, 2011; Smittenaar et al., 2013). Indeed, higher activation of the dlPFC for the stop relative to the ignore condition in the *dDts* strategy was also observed in a previous stimulus-selective stopping study using ERP in conjunction with LORETA source reconstruction procedures (Sánchez-Carmona et al., 2016).

It should also be noted that stopping-related activation was primarily observed in left-lateralized cortical regions. Although global stopping typically involved a right-hemisphere network, bilateral and left-lateralized activation has also been reported (Albert et al., 2013; Hirose et al., 2012; Li et al., 2006; Swick et al., 2008; Zhang and Li, 2012). We speculate that discriminating between stop and ignore signals before the suppression of the response in selective stop-signal tasks could induce a more serial form of processing compared to non-selective stop-signal tasks, which do not involve such discrimination. This serial processing would trigger resetting operations in working memory linked to the activation of brain structures in the left rather than in right frontal cortices.

Although the successful stop versus ignore comparison seems to overcome some of the limitations of traditional contrasts, the contribution of motor response effects could not be totally ruled out since stop - but not ignore - trials involve motor response execution. Thus, it would be possible that the high-beta effect observed in the *dDtS* strategy may reflect motor preparation or response execution instead of selective stopping. Indeed, beta oscillations are strongly believed to be implicated in motor response execution (Engel and Fries, 2010; Kilavik et al., 2013). However, there are several reasons that suggest that the increased activation in the beta band observed here could be primarily linked to response cancellation. First, differences between the successful stop and ignore conditions in the selective response cancellation group (*dDtS*) were only found in the high-beta frequency band, and only near the end of the SSRT (i.e., just at the time when the motor response is estimated to be cancelled in this strategy). Second, as expected, no differences were observed in the high-beta band between the successful stop and ignore conditions in the *StD* group, where response cancellation is thought to be non-selectively activated in both conditions (Bisset and Logan, 2014). Third, the increased high beta band activity observed in the *dDtS* group was estimated to arise from regions typically associated with stopping (the preSMA) rather than with responding.

Nevertheless, in order to get further evidence for the involvement of high-beta band in response cancellation, we performed an ad hoc analysis comparing activity in the ignore condition in the *StD* and the *dDtS* strategies. Of note, ignore trials in the *StD* strategy involve firstly response cancellation and subsequently response execution, whereas ignore trials in the *dDtS* only involve response execution (in this strategy, individuals do not inhibit their responses within this condition: (Bissett and Logan, 2014). As expected, we found greater activity in the high-beta band in the *StD* than in the *dDtS* strategy. This increased activity emerged at the end of the SSRT in the *StD* (i.e., just at the time when the motor response is thought to be cancelled in this strategy). Remarkably, unlike results reported in the stop versus ignore comparison in the *dDtS* strategy, these effects lasted for several hundred milliseconds, indicating that the comparison between ignore trials in both strategies involves additional processes beyond response cancellation. Thus, although these data also argues for a role of high-beta activity in response cancelation, some caution is needed when interpreting this scarcely explored functional comparison.

In summary, present results contribute to our understanding of the neural mechanisms underlying selective stopping strategies. We found that a successful cancelation of an initiated response is specifically associated with an increased oscillatory activity in the high-beta frequency band in the strategy characterized by stopping selectively (*dDtS*), but not in the strategy characterized by stopping non-selectively (*StD*). These findings provide further neural support for the existence of different strategies for successfully performing stimulus-selective stopping tasks (Bissett and Logan, 2014; Sánchez-Carmona et al., 2016; Sebastian et al., 2017). Moreover, they provide evidence suggesting that high-beta oscillations in medial superior and middle frontal cortices may constitute an important neural marker of response cancellation.

Conflicts of interest

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.04.066.

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Supplementary Material

A dimensional classification of selective stopping strategies, and correlational analyses with neural oscillatory features

Following a Reviewer's suggestion, we analyzed selective stopping strategies following a dimensional approach. First, each participant was placed in a 3D space, each dimension representing the mean go, failed-stop and ignore reaction time. Thereafter, we plotted a cut-off surface that leaves above it all *Stop then Discriminate* (*StD)* participants and below it, all *dependent Discriminate then Stop* (*dDtS)* participants. Interestingly, the whole sample formed a continuum. We then reformulated this representation in order to simplify its interpretation. Concretely, given that the ignore RT dimension is not critical to distinguish between strategies (Bisset & Logan, 2014), it was removed from the representation. Thus, only go and failed stop RTs were finally considered in the analysis to define the location of each participant in a 2D space (see Figure below). For a correct interpretation of the *StD-dDtS* dimension, the theoretical cut-off between strategies was also represented as the line of equivalent failed stop RTs and go RTs. Hypothetically, the closer to such edge, the more representative of *dDtS* strategy a participant would be; conversely, the more distant to this theoretical edge, the more representative of *StD* strategy a participant would be. Then, we tried to associate the euclidean distance between the 2D location of each participant and this theoretical edge with several neural correlates. The regression residuals did not significantly correlate with any neural oscillatory feature (i.e., the amplitude of successful stop high-beta desynchronization or the relative difference between successful stop and ignore high-beta oscillations). Thus, we did not find significant correlations with oscillatory measures associated with response cancellation using a dimensional approach of selective stopping strategies.

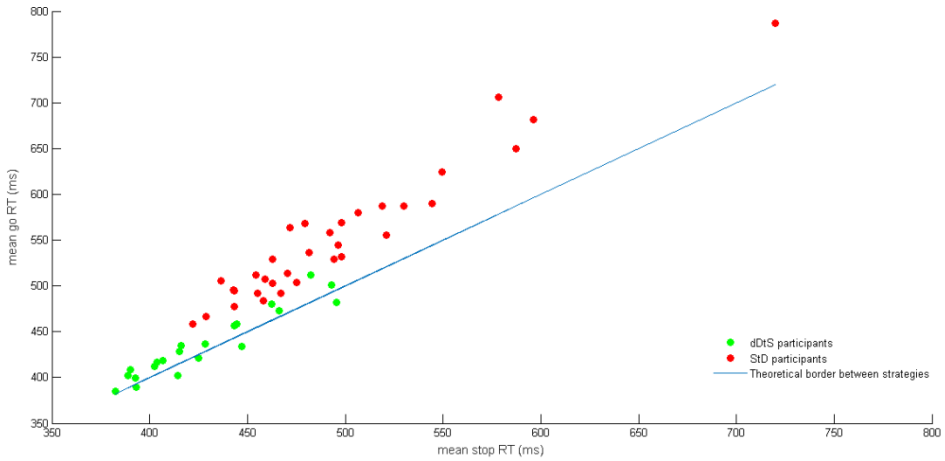
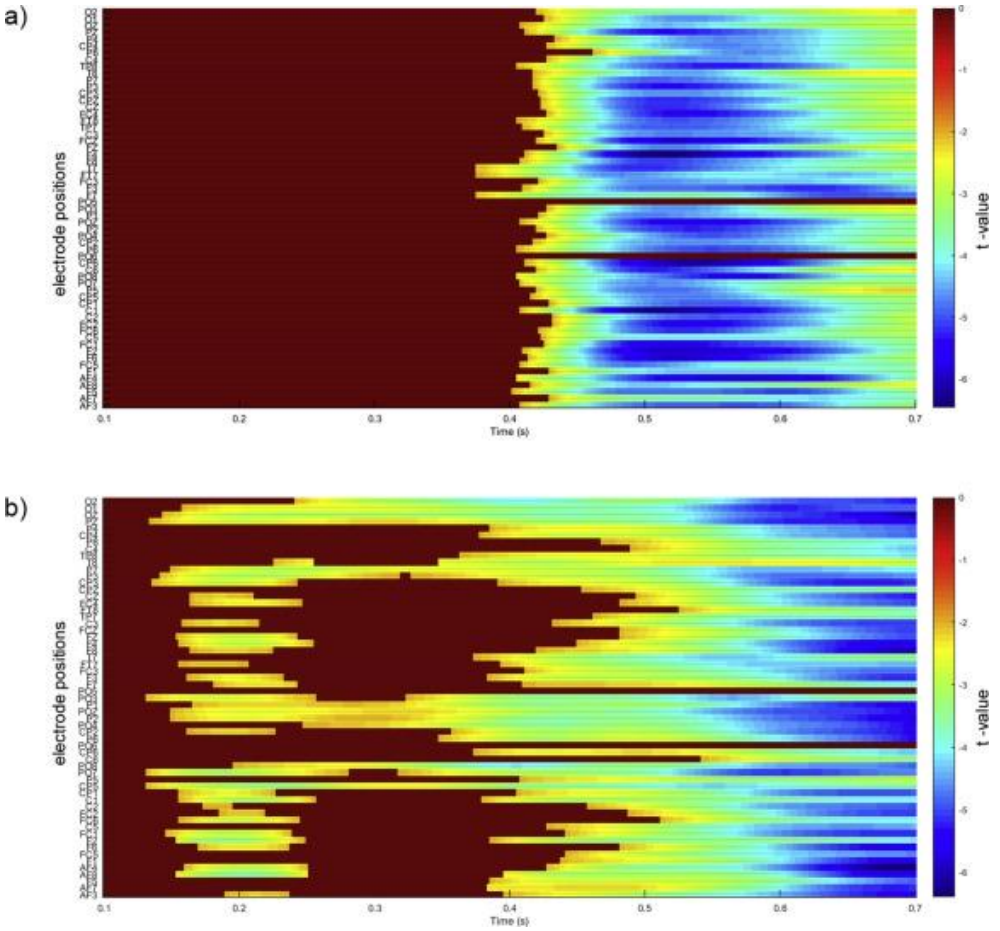
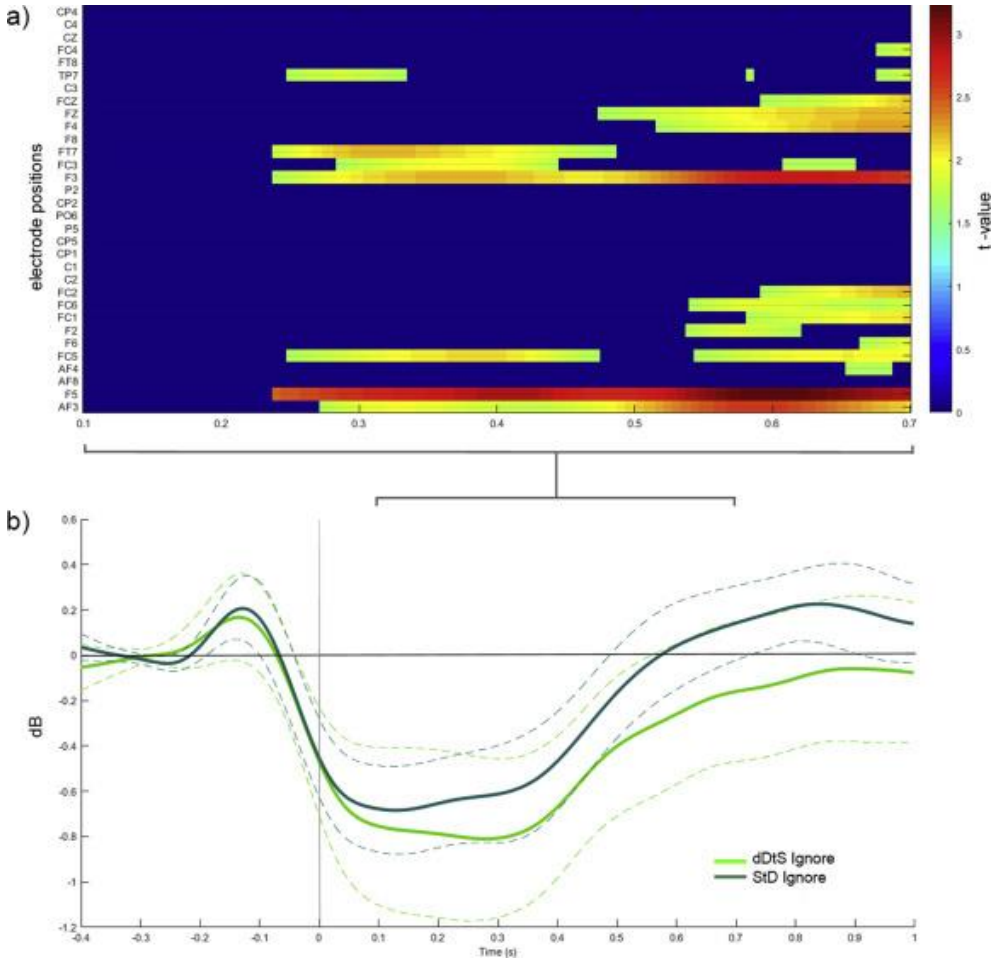


Figure. 2D space of mean go and failed-stop RTs (mean ignore RTs was removed for easy interpretation). Red and green dots represent *StD and dDtS* participants respectively, and the blue line represents the theoretical edge between strategies, in which mean failed-stop and go RTs would be completely equal.

Supplementary Figures



Sup Figure 1. a) Negative significant clusters of non-parametrical permutation analysis in theta (a) and low-beta (b) frequency bands for the successful stop versus successful ignore comparison in the *Stop then Discriminate (StD)* strategy (i.e., greater power for successful ignore compared to successful stop condition was found). Color bar represents t values.



Sup Figure 2. a) Positive significant clusters of non-parametrical permutation analysis in high-beta frequency band (21-30 Hz) showing greater power for successful ignore trials in the *Stop then Discriminate* (StD) strategy compared to successful ignore trials in the *dependent Discriminate then Stop (dDtS)* strategy. Color bar represents t values. b) Time course of total high-beta power, averaged for significant electrodes, comparing ignore conditions between strategies. Dashed lines represent 95% confidence interval.

4.3 Conclusiones

- Las dinámicas oscilatorias relacionadas con la cancelación de una respuesta motora (ritmo beta-alto y giro frontal superior y medial, incluyendo el área motora presuplementaria) se observaron en la estrategia caracterizada por inhibir selectivamente (*DPd*) pero no en la estrategia caracterizada por inhibir no selectivamente (*PD*).

- El ritmo beta-alto, pero no los ritmos beta-bajo y theta, se asociaron específicamente con la cancelación de una respuesta motora. En concreto, se observó una mayor energía de las oscilaciones en beta-alto en la condición *stop-acierto* en comparación con la condición *ignorar* en la estrategia caracterizada por inhibir selectiva ante la señal *stop* pero no ante la señal *ignore* (*DPd*).

5 DISCUSIÓN GENERAL

Los resultados de la presente tesis doctoral suponen un importante paso adelante en la caracterización neural y conductual de la inhibición selectiva a nivel de estímulo, un tipo de inhibición escasamente explorada que, sin embargo, juega un papel relevante en nuestra vida cotidiana. De hecho, se trata de la primera evidencia acerca de la existencia de diferentes patrones de activación cerebral asociados a la distinción conductual de las estrategias establecida por Bisset y Logan (2014). Los resultados obtenidos respaldan las hipótesis planteadas por estos autores sobre la existencia de diferencias estrategias para resolver satisfactoriamente una tarea de inhibición selectiva a nivel de estímulo. Asimismo, los resultados de esta tesis contribuyen a un mejor conocimiento sobre los mecanismos neurales implicados específicamente con el proceso de interrupción de una respuesta motora. Los hallazgos encontrados podrían ayudar a una mejor comprensión de la inhibición y la impulsividad en la población general, así como contribuir a una mejor caracterización de las dificultades inhibitorias observadas en varios trastornos clínicos como el trastorno por déficit de atención con hiperactividad, el trastorno límite de la personalidad o el abuso de sustancias.

En primer lugar, los resultados obtenidos muestran la utilidad del procedimiento descrito por Bisset y Logan (2014) para identificar y clasificar las distintas estrategias cognitivas empleadas por los participantes para resolver una tarea de inhibición selectiva (esto es, comparando los TRs asociados a cada tipo de ensayo: *go*, *continuar* y *stop*). En los dos estudios de esta tesis doctoral se identificó adecuadamente la estrategia adoptada por cada participante para enfrentarse a la tarea experimental. Sin embargo, se debe señalar que la proporción de participantes que escogieron cada tipo de estrategia varió con respecto a lo encontrado por Bisset y Logan (2014) en su revisión de ocho estudios previos que habían empleado un paradigma de inhibición selectiva sin tener en cuenta las distintas estrategias para resolver la tarea (véase Tabla 2 de Bisset y Logan, 2014).

En concreto, mientras que sólo un 6% de los participantes se vinculaban con la estrategia *DPi*, en nuestros datos todos aquellos participantes en los que se identificó inicialmente esta estrategia fueron descartados finalmente después de aplicar varios procedimientos dirigidos a garantizar la fiabilidad de los datos conductuales de cada participante. Más allá de su precisión o de su velocidad de repuesta, se examinó también el ajuste lineal de las funciones de inhibición de cada participante. La función de inhibición describe cómo varía la probabilidad de cometer un fallo inhibitorio conforme la demora (*SSD*) entre los estímulos *go* y *stop* aumenta. Así, un correcto desempeño en la tarea debería reflejarse en una función de inhibición creciente, hasta alcanzar una probabilidad p=1 asociada a la demora más larga que haya experimentado el participante en la tarea (Verbruggen y Logan, 2009). Sin embargo, dada la naturaleza de la *tarea stop-signal*, los participantes deben lidiar con la ambigüedad de garantizar una respuesta rápida ante los estímulos *go* al mismo tiempo que un adecuado desempeño en los ensayos stop, sabiendo que no es posible inhibir correctamente la respuesta en todos los ensayos stop (la tarea está diseñada para que cada participante obtenga aproximadamente un 50% de inhibiciones correctas ante la señal *stop*). Así, algunos participantes no dieron muestras de tolerar el error, enlenteciendo voluntaria o involuntariamente sus respuestas ante los

estímulos *go* con el fin de reducir los fallos inhibitorios ante la aparición repentina e infrecuente de la señal *stop*. Esta probable variación intencional de la velocidad quedaba reflejada en funciones de inhibición no lineales que, de hecho, introducen sesgos en la estimación del tiempo medio de inhibición de estos participantes. De este modo, es posible que la aplicación de este criterio de selección pueda ser una herramienta útil para futuros estudios que empleen esta tarea experimental e incluso que, de haber sido aplicado sobre los estudios analizados por Bisset y Logan, se hubiera reducido aún más la tasa de participantes identificados bajo la estrategia *DPi*.

Por su parte, la proporción de participantes que utilizaron las dos estrategias restantes difirió notablemente con respecto a lo hallado y revisado por Bisset y Logan (2014). Mientras que la mayor parte de los participantes de los estudios previos emplearon la estrategia *DPd*, los participantes de los dos estudios de esta tesis doctoral utilizaron mayoritariamente la estrategia *PD*. Ante tal observación conviene reseñar que, dado que uno de los objetivos del presente trabajo era aislar los correlatos electrofisiológicos del propio proceso inhibitorio, se buscó minimizar las diferencias entre los estímulos *stop* e *ignorar* con el fin de no introducir factores adicionales que pudieran explicar las diferencias electrofisiológicas entre estas dos condiciones experimentales. Así, mientras que en el presente trabajo la única dimensión en la que diferían ambos estímulos remitía a la orientación de la figura utilizada como estímulo (rombo frente a cuadrado), lo más frecuente en el campo de la inhibición selectiva ha sido que los estímulos *stop* e *ignorar* difieran en color. Podría esperarse que una mayor dificultad para discriminar entre estos dos tipos de estímulos pudiera llevar a una mayor cantidad de participantes a la adopción de una estrategia más conservadora, interrumpiendo su respuesta preliminarmente para después discriminar los estímulos en cuestión. Por el contrario, en aquellos casos en los que resulte sencillo discriminar entre ambos estímulos, es posible que una mayor cantidad de participantes opten por desempeñar esta labor de discriminación sin necesidad de detener previamente su respuesta. Esta hipótesis se evaluó a través de un estudio conductual no incluido en esta tesis doctoral que está actualmente en proceso de publicación (Sánchez-Carmona, Rincón-Pérez, López-Martín, Albert e Hinojosa, en revisión). En esta investigación, 72 participantes realizaron una tarea de inhibición selectiva a nivel del estímulo compuesta por distintos bloques experimentales que diferían en el tipo de estímulos presentados. Así, en unos bloques los estímulos empleados para los ensayos *stop* e *ignorar* diferían solo en la forma, mientras que en otros bloques los estímulos diferían tanto en forma como color, variando así la dificultad con la que podían discriminarse. Los resultados obtenidos mostraron que en aquellos bloques en los que los estímulos *stop* e *ignorar* se diferenciaban en forma y color, la estrategia mayoritariamente adoptada por los participantes era la estrategia *DPi*. Por el contrario, en los bloques en los que los estímulos stop e ignore se diferenciaban sólo en forma, los participantes elegían principalmente la estrategia PD. Estos datos sugieren en un diseño intra-sujetos que los participantes pueden cambiar la estrategia que adoptan para resolver la tarea de inhibición selectiva a nivel de estímulos en función de variables externas relacionadas con la dificultad que conlleve la discriminación perceptiva entre estímulos.

En cualquier caso, la distinción y descripción de las diferentes estrategias que pueden emerger en la resolución de una tarea de inhibición selectiva a nivel del estímulo propuesta por Bisset y Logan, remite exclusivamente al dominio conductual. De este modo, los datos de la presente tesis doctoral contribuyen también a ofrecer un mayor respaldo a la distinción de estas estrategias, ya que han podido observarse diferentes patrones de activación cerebral relacionados con cada estrategia. Así, los datos obtenidos señalan que la distinción propuesta por Bisset y Logan (2014) no sería una mera especulación conceptual, ya que cada estrategia se caracteriza por un patrón electrofisiológico específico y acorde con las hipótesis establecidas a partir de los resultados conductuales. De forma general, ha podido observarse que, con independencia del tipo de contraste funcional empleado, los datos neurales obtenidos muestran que la estrategia *PD* se asocia, en comparación con la estrategia *DPd*, con una activación neural más global (implica a un mayor número de posiciones de electrodos) y más intensa (genera una mayor amplitud de los PER y una mayor energía de los ritmos oscilatorios).

Como se ha adelantado anteriormente, en los últimos años han surgido algunas críticas acerca de la conveniencia de emplear los contrastes más comúnmente utilizados para aislar los correlatos neurales de la interrupción de una respuesta motora. Mientras que gran parte de la literatura ha optado por comparar los ensayos *go* y los ensayos *stop-acierto*, varios estudios plantean que esta comparación podría resultar excesivamente inespecífica, ya que estos dos ensayos no solo difieren en el proceso de interés (la inhibición de respuesta), sino también en el procesamiento perceptivo y atencional (Albert, López-Martín, Hinojosa y Carretié, 2013; Boehler et al., 2010; Dimoska et al., 2006; Etchell et al., 2012; Li et al., 2006, Sharp et al., 2010). Ante tales dificultades, otros estudios han optado por interpretar los correlatos neurales de la interrupción de una respuesta en términos de las diferencias observadas entre el contraste *stop-acierto* (respuestas correctamente inhibidas) versus *stop-fallo* (respuestas no inhibidas, fallos inhibitorios). No obstante, esta comparación funcional podría ser demasiado restrictiva al estar presente el proceso de interés (la inhibición) en ambas condiciones (Boheler et al, 2010) e incluso podrían interferir procesos relacionados con la detección y supervisión del error que solo se observarían en una de las condiciones (Li et al., 2006). De hecho, de acuerdo con el propio *modelo independiente de carrera de caballos*, la condición *stop-acierto* no sería directamente comparable con ninguna de las dos condiciones anteriormente expuestas por una connatural diferencia en la latencia y duración de los procesos implicados. Mientras que en la condición de aciertos inhibitorios (*stop-acierto*), el proceso de respuesta (*go*) subyacente sería necesariamente más lento que aquel propio de toda la distribución go/de respuesta, dicho proceso sería más rápido en los ensayos de fallo inhibitorio que en los ensayos de acierto inhibitorio. Por ello, con el fin de reducir las limitaciones de los contrastes funcionales tradicionales, se seleccionaron los ensayos *go* y los ensayos *stop-fallo* más lentos (esto es, con TR más elevados al promedio de su distribución). De esta forma, otra de las aportaciones de esta tesis doctoral fue comparar el grado de especificidad de cada contraste funcional a la hora de examinar la actividad electrofisiológica asociada con la interrupción de una respuesta motora ya iniciada.

Pese a las consideraciones anteriormente mencionadas, el contraste entre los ensayos *go* y los ensayos *stop-acierto* continuó resultando altamente inespecífico. Por su parte, el contraste entre los ensayos *stop-acierto* y *stop-fallo* se mostró también excesivamente restrictivo, revelando diferencias que no podían asociarse temporalmente con el proceso de cancelación de una respuesta según su estimación mediante el modelo de carrera de caballos (las diferencias electrofisiológicas se localizaron antes de la finalización del tiempo estimado de inhibición o *SSRT*). Por el contrario, en ambas estrategias los resultados obtenidos a partir de la nueva comparación funcional de los ensayos *stop-acierto* y los ensayos *ignorar* fueron más específicos, mostrando diferencias en la activación neural entre condiciones que se localizaban temporalmente alrededor de la latencia estimada por el modelo de carrera de caballos para el tiempo medio de inhibición o *SSRT*. Estas diferencias electrofisiológicas entre condiciones aludían a correlatos electrofisiológicos previamente asociados con la interrupción de respuestas motoras en paradigmas de inhibición simple o global. Por lo tanto, los datos de la presente tesis doctoral apuntan a que el mejor contraste funcional para aislar el proceso de interrupción de una respuesta motora (minimizando así la interferencia de factores periféricos a dicho proceso cognitivo), es la comparación entre la condición stop-acierto y la condición ignorar dentro de un paradigma de inhibición selectiva.

Tomando como marco de referencia el patrón de diferencias estadísticamente significativas observadas para cada estrategia en esta comparación funcional (*stop-acierto* vs. *ignorar*), es posible extraer conclusiones acerca de la diferente implicación del proceso de interrupción de respuesta en cada una de ellas. Estos datos apoyarían la descripción conductual de las estrategias realizada por Bisset y Logan (2014). Como puede observarse en los resultados del primer estudio de esta tesis doctoral, el análisis univariado masivo de los PER para cada comparación funcional tradicional mostró que únicamente el P3 era sensible a las manipulaciones experimentales, mostrando una mayor amplitud en la condición stop-acierto que en el resto de las condiciones en donde se supone que el proceso de cancelación no se produce o se produce con una menor intensidad. Por tanto, según estos resultados, P3 sería el componente de los PER más relacionado con el proceso específico de interrupción de la respuesta motora. Además, estos datos apoyarían la hipótesis que actualmente tiene un mayor respaldo experimental en este ámbito de conocimiento, que asocia a P3 en lugar de N2 con el proceso de inhibición, al menos en población adulta (Enríquez-Geppert et al., 2010; Albert et al., 2013). Sin embargo, como se ha manifestado anteriormente, los efectos observados en cada uno de estos contrastes tradicionales eran muy inespecíficos y no podían integrarse con los datos conductuales relativos a la latencia del tiempo medio de inhibición o *SSRT*. Todo ello sugería que la comparación entre los ensayos *stop-acierto* e *ignorar* podía representar la mejor opción para examinar de manera específica los correlatos electrofisiológicos de la cancelación de una respuesta. En concreto, los datos relativos a nuestro primer estudio revelaron que el inicio de las diferencias entre las condiciones *stop-acierto* e *ignorar* en la estrategia *DPd* se localizan en el inicio del componente P3, resultado que concuerda con los datos obtenidos por Wessel y Aron (2015). Cabe destacar que la latencia estimada del inicio de estas diferencias no difería de la latencia estimada del tiempo medio de inhibición estimado para esta estrategia (calculado, como proponen

Bisset y Logan (2014), sobre la distribución de los tiempos de reacción de la condición *ignorar*). Asimismo, los datos relativos al análisis de localización de fuentes con sLORETA/eLORETA asociaron estos efectos observados en la superficie del cuero cabelludo con la activación de un conjunto de regiones corticales entre las que destacaban el giro frontal inferior (área de Brodmann, AB, 44/45), la CPFDL (AB 46/9/8), la ínsula (AB 13) y el lóbulo parietal superior (AB 7). La activación se observó predominantemente en el hemisferio izquierdo. Como puede observarse, la implicación de este conjunto de regiones va más allá de la propia activación de la región clave en el estudio de la inhibición global de una respuesta (giro frontal inferior), lo que señalaría que la interrupción selectiva de una respuesta dependería más bien de la activación de una red funcionalmente heterogénea de regiones cerebrales. Así, dentro de esta red de parada selectiva (Aron, 2011), podría destacarse el papel diferencial de la CPFDL, una región clave para la memoria de trabajo (Müller y Knight, 2006). Estudios de imagen por tensor de difusión muestran que esta región estaría conectada con la cabeza del núcleo caudado (Lehéricy et al., 2004), por lo que se ha propuesto que la interrupción selectiva de una respuesta podría ser implementada por medio de un circuito CPFDL-frontal-ganglios basales, apoyado en el funcionamiento de la vía indirecta del movimiento (Aron, 2011). En concreto, la meta del participante acerca de cómo debe comportarse ante los estímulos de la tarea estaría implementada a nivel neural en una señal que sería enviada desde la CPFDL hasta el estriado, con el objetivo de inhibir la sección externa del globo pálido, que por su parte retiraría carga inhibitoria de la parte interna del globo pálido (de forma directa o a través del núcleo subtalámico) y todo ello finalmente incrementaría la inhibición sobre representaciones motoras corticales discretas (Figura 5).

Por su parte, en la estrategia *PD*, en la que se hipotetiza que el proceso de interrupción de respuesta estaría presente tanto en los ensayos *stop-acierto* como en los ensayos *ignorar*, los datos del análisis univariado masivo de los PER corroboraron la ausencia de diferencias significativas entre estos dos tipos de ensayos alrededor del tiempo estimado de inhibición (*SSRT*). Por tanto, estos resultados apoyan la hipótesis establecida de que los participantes que adoptan esta estrategia interrumpen sus respuestas de una manera no selectiva ante la señal *stop* y ante la señal *ignorar*. Se debe señalar que, aunque en la presente tesis se observaron diferencias entre condiciones en esta estrategia, éstas solo emergieron después del *SSRT* estimado y se localizaron en regiones del cuero cabelludo posteriores que no han sido previamente relacionadas con el proceso de inhibición. Por ello, es muy improbable que estos efectos puedan vincularse con la cancelación de la respuesta motora. Por tanto, la evidencia cruzada de los datos de los PER obtenidos en cada estrategia sugiere que la cancelación de las respuestas motoras se realiza de forma selectiva en la estrategia *DPd* y de manera no selectiva (inespecífica) en la estrategia *PD*. La inmediata consecuencia de esta conclusión es que estos datos respaldan la descripción conductual de las estrategias planteada por Bisset y Logan (2014), así como también la delimitación de un procedimiento experimental idóneo para estudiar las bases neurales específicamente asociadas con la interrupción de una respuesta motora a través del uso conjunto de un paradigma de inhibición selectiva y un contraste funcional que implique la comparación de la condición *stop-acierto* y la condición i*gnorar* en la estrategia *DP*.

Basándose en los hallazgos encontrados en el primer experimento, el segundo estudio de esta tesis tenía como objetivo seguir caracterizando los patrones de activación neural asociados con el proceso de interrupción de respuesta en cada una de las estrategias implicadas en una tarea de inhibición selectiva a nivel de estímulo. Para ello, se utilizó el mismo paradigma experimental empleado en el primer experimento, pero en esta ocasión se examinaron las dinámicas oscilatorias relacionadas con cada estrategia. Como se ha señalado, aunque parten de una misma señal de registro de la actividad cerebral (el EEG), los PER y las oscilaciones proporcionan distinta información sobre la actividad neural que subyace al proceso de estudio. De nuevo, mientras que en la estrategia *PD* no se observaron diferencias significativas en la energía de los ritmos típicamente relacionados con la cancelación de una respuesta motora (theta y beta: Jha et al., 2015; Isabella et al., 2015; Swan et al., 2009; 2012), las diferencias emergieron en la estrategia *DP*. En particular, se encontraron diferencias significativas en la energía correspondiente al ritmo beta-alto (21-30 Hz) entre la condición *stop-acierto* e *ignorar*, cuyo origen cortical se estimó en la corteza frontal medial superior, incluyendo al área motora presuplementaria, Como se ha señalado, el área motora presuplmentaria representa junto con el giro frontal inferior, una de las dos regiones más consistentemente implicadas en el proceso de inhibición. Específicamente la activación de esta región se ha relacionado con la interrupción de una respuesta dominante o ya iniciada. Se debe señalar además que las diferencias en beta-alto se localizaron temporalmente alrededor del tiempo estimado de inhibición para esa estrategia, lo que apoyaría también la hipótesis de que este ritmo juega un papel fundamental en la cancelación de repuesta (Swan et al., 2009; Aron, Herz, Brown y Forstmann, 2016). Además, de acuerdo con el marco conceptual desarrollado a partir de la descripción conductual de las estrategias, se llevó a cabo una comparación funcional a posteriori para respaldar la implicación de las oscilaciones en beta-alto en el proceso de cancelación de una respuesta motora. En concreto, se comparó la energía de este ritmo observada en los ensayos *ignore* de la estrategia *PD* (en donde se estima que se ha activado el proceso de inhibición) con la energía observada en los ensayos ignore de la estrategia *DPd* (en donde no se estima que se haya producido inhibición). Se encontró una mayor energía alrededor al tiempo estimado de inhibición de la estrategia *PD* en comparación con la estrategia *DPd*, lo que sugiere la implementación del proceso de interrupción de la respuesta en la estrategia en donde se espera que se observe este proceso.

Con todo, dada la idoneidad de incorporar la condición *ignorar* como control experimental para superar las limitaciones de los contrastes clásicamente empleados en la literatura para estudiar los correlatos neurales de la interrupción de respuestas motoras, los datos de la presente tesis doctoral también contribuyen a profundizar no solo en el estudio de la inhibición selectiva sino también en el estudio de los correlatos neurales del proceso de cancelación de una respuesta. No obstante, como ha podido observarse, la mera introducción de esta nueva condición experimental en un paradigma de inhibición selectiva no garantiza que la interrupción de respuestas motoras emerja en todos los participantes. Por ello, resulta imprescindible identificar primero las estrategias empleadas por cada uno de ellos para posteriormente seleccionar únicamente aquellos que hayan adoptado la estrategia *DP*, ya sea independiente o dependiente. Según los

resultados de esta tesis, los participantes que escogen la estrategia *PD* interrumpen sus respuestas motoras indiscriminadamente ante las señales presentadas (*stop* e *ignorar*), impidiendo el aislamiento del proceso objeto de estudio. De este modo, resulta probable que los correlatos neurales observados en la presente tesis doctoral como índices de la interrupción selectiva de una respuesta motora supongan también los mejores candidatos para representar los mecanismos electrofisiológicos vinculados específicamente con la interrupción de respuestas motoras simples o globales. No obstante, es preciso tener en cuenta que la inhibición selectiva, en comparación con la simple o global, probablemente active otras regiones cerebrales al ser más compleja e implicar procesos adicionales. En este contexto, varias de las regiones observadas en la presente tesis como la CPFDL o la ínsula podrían estar jugando un papel más general que el de participar en el proceso específico de interrupción de una respuesta motora ya iniciada.

Por último, se debe señalar que la presente tesis doctoral ha intentado sacar provecho de diversos procedimientos metodológicos relacionados con el preanálisis y análisis de la señal EEG con el fin de dar una mejor respuesta a los objetivos planteados. En el primer estudio, se empleó el análisis univariado masivo (Groppe, Urbach y Kutas, 2011), uno de los procedimientos más precisos (según nuestro conocimiento) para delimitar el inicio y la finalización de los efectos observados en los PER. Este tipo de análisis, por tanto, explota la alta resolución temporal de los PER, un aspecto relevante en el estudio de la inhibición porque el proceso de interrupción de una respuesta motora se observa en latencias menores al medio segundo y tiene una duración muy corta que no va más allá de los 100-300 milisegundos. Además, el análisis univariado masivo tiene la ventaja frente a otros procedimientos empleados en el análisis de los PER, de poder examinar posibles diferencias sin ninguna asunción a priori, siendo un procedimiento completamente ciego a las expectativas del experimentador. Por su parte, en lo que respecta a la metodología del segundo experimento de esta tesis, una vez identificado el mejor contaste funcional para aislar el proceso de interés, se exploraron las posibles diferencias en los ritmos oscilatorias utilizando también un procedimiento imparcial con respecto al respecto al momento temporal y localización de los cambios de potencia inducidos por cada estímulo. Así, para solucionar el problema de las comparaciones múltiples, se emplearon pruebas de permutación no paramétricas basadas en clusters (Maris y Oostenveld, 2007; Cohen, 2014), contrastando la probabilidad de los efectos observados con una distribución de hipótesis nula aleatoria pero basada en la naturaleza de los propios datos experimentales. Empleando este tipo de análisis con un menor número de apriorismos, los resultados obtenidos en esta tesis doctoral sugieren, en la misma línea que Bisset y Logan (2014), que no todos los participantes que llevan a cabo una tarea de inhibición selectiva hacen lo que los examinadores creen que debían estar haciendo (esto es, inhibir selectivamente). Por el contrario, un conjunto de personas parece resolver esta tarea mediante una estrategia cognitiva que implica inhibir de manera no selectiva. Los datos de actividad cerebral muestran que estas diferentes estrategias se asocian con distintos patrones electrofisiológicos, observados tanto en los PER como en las dinámicas oscilatorias, y tanto en la superficie (cuero cabelludo) como a nivel de vóxel (regiones corticales activadas).

6 CONCLUSIONES GENERALES

- Se observó un patrón de actividad electrofisiológica distinto entre la estrategia caracterizada por inhibir selectivamente ante la señal *stop* pero no ante la señal *ignorar* (*DPd*) y la estrategia caracterizada por inhibir de manera no selectiva ante ambos tipos de señales (*PD*). En concreto, los correlatos electrofisiológicos relacionados con el proceso de cancelación de una respuesta pudieron observarse en la estrategia *DPd* pero no en la estrategia *PD* cuando la condición *stop-acierto* se comparó con la condición *ignore* en cada una de las estrategias. Estos resultados apoyan a través de distintas medidas de actividad cerebral la existencia de las estrategias propuestas por Bissett y Logan (2014) a nivel conductual.

- El inicio del componente P3, las oscilaciones en beta-alto y la activación de distintas regiones corticales principalmente ubicadas en el lóbulo frontal (giro frontal inferior, área motora presuplementaria y corteza prefrontal dorsomedial) se mostraron como los correlatos neurales del proceso de cancelación de una respuesta motora. La comparación entre las condiciones *stop-acierto* e *ignore* en la estrategia caracterizada por inhibir selectivamente (*DP*) se mostró como el mejor procedimiento para aislar la actividad electrofisiológica específicamente relacionada con la cancelación de una respuesta. A nivel de superficie, P3 pero no N2 y beta (alto) pero no theta se asociaron con la inhibición de una respuesta ya iniciada, lo que sugiere que N2 y theta podrían jugar un papel más general (no vinculado específicamente con la supresión de una respuesta) en las tareas de inhibición selectiva. A nivel de vóxel, tanto el giro frontal inferior como el área motora suplementaria, fueron las regiones principalmente implicadas en la interrupción de la repuesta, hallazgo que está en consonancia con lo observado por los estudios de inhibición simple o global. La activación de la CPFDL observada en nuestros estudios (un área típicamente no relacionada con el proceso de cancelación de respuesta) podría explicarse por las demandas adicionales que genera la inhibición selectiva frente a la inhibición simple.

7 LIMITACIONES Y LÍNEAS FUTURAS

La presente tesis doctoral no está exenta de limitaciones que deben tenerse en cuenta para interpretar apropiadamente en contexto los resultados obtenidos y para establecer las líneas futuras de investigación en este ámbito de conocimiento. En primer lugar, dados los objetivos planteados en la presente tesis doctoral, podría haber resultado provechoso comparar la condición de *stop-acierto* entre estrategias. Sin embargo, una importante limitación del presente trabajo remite a la imposibilidad de realizar esta comparación como consecuencia de la diferencia existente entre ambas condiciones en la latencia de los procesos implicados, ya que el proceso de cancelación de la respuesta resulta significativamente más rápido en la estrategia *PD* que en la estrategia *DPd* (Bisset y Logan, 2014).

En segundo lugar, no puede obviarse que, aunque la condición *ignorar* representa posiblemente la mejor condición de control con respecto a la condición *stop-acierto*, ambas continúan difiriendo en la propia emisión de la respuesta motora, lo que podría introducir algunos efectos no relacionados con el objeto de estudio. Sin embargo, esta limitación resulta inherente a todas las posibles comparaciones que pudieran emplearse para examinar los correlatos cerebrales de la interrupción de respuestas motoras, dado que en cualquier caso sería necesario comparar una condición en la que una respuesta sea interrumpida satisfactoriamente y otra condición en la que la respuesta sea finalmente expresada.

En tercer lugar, la descripción conductual de las estrategias planteada por Bisset y Logan (2014) remite a procesos tan específicos como los asociados a la emisión de las respuestas, a su interrupción o a la propia discriminación de los estímulos *stop* e *ignorar*. Sin embargo, la clasificación de las estrategias se realiza a partir de la media de los TR de cada tipo de ensayo que el participante muestra globalmente en la tarea. Dado que las técnicas dirigidas a identificar los correlatos neurales asociados a dichos procesos cognitivos empleadas en la presente tesis doctoral también operan sobre el promedio de las mencionadas condiciones experimentales, sería interesante tratar de reproducir los presentes hallazgos mediante estrategias de análisis de la actividad EEG ensayo a ensayo.

En cuarto lugar, resulta evidente que los procesos cognitivos que pueden diferir entre las diferentes estrategias entre las que se puede optar para realizar correctamente la tarea de inhibición selectiva a nivel del estímulo trascienden a la propia interrupción de respuestas. Cabría esperar que entre ambas estrategias pudieran existir diferencias que puedan remitir a otros procesos ejecutivos como la atención, la memoria de trabajo o la capacidad para automatizar la tarea. Por ello, futuras investigaciones deberán abordar cuáles de estos procesos pueden diferir entre las estrategias y, consecuentemente, cuáles son sus correlatos neurales. Esta cuestión remite de hecho a la relevante pregunta acerca de qué factores ocasionan que un participante se acoja a una u otra estrategia. Bisset y Logan (2014) ya reportaron la posibilidad de que aspectos intrínsecos de la tarea, como la tasa relativa de presentación de los estímulos *stop e ignorar*, puedan influir en la selección de la estrategia. Así, cuanto más frecuente resulte la necesidad de interrumpir una respuesta, más probable es que los participantes se vinculen con la estrategia de *PD*, mientras que cuanto menos frecuente resulte, más probable es que los participantes adopten la estrategia Discriminar Parar, lo que indicaría que la

primera estrategia se asocia a un estilo de resolución más conservador, mientras que la segunda se relacionaría con una estrategia más arriesgada. Estos datos también señalan que los mismos participantes pueden acogerse a una u otra estrategia de forma flexible en función de esta alteración del contexto de la tarea. En esta línea, los datos de la investigación de la dificultad en la discriminación de los estímulos de inhibición e ignorar/continuar, también parecen señalar que este factor puede sesgar la selección de la estrategia y de hecho, también de forma flexible. Dada esta evidencia, resulta imprescindible que futuras investigaciones traten de esclarecer que otros factores intrínsecos de la tarea pueden afectar a la selección de las estrategias. Del mismo modo, podría esperarse que ciertas características de los propios participantes puedan influir también en la estrategia que adopten a la hora de enfrentar este tipo de tarea. En este sentido, los resultados de un estudio conductual llevado a cabo por nuestro grupo de investigación sugieren que la elección de estrategias podría también diferir en función de factores genéticos inherentes al propio individuo (Rincón-Pérez et al., en preparación).

Finalmente, el empleo del EEG en combinación con algoritmos de localización de fuentes neurales de la actividad no permite examinar la participación de regiones subcorticales y su interacción con regiones corticales en la inhibición selectiva a nivel de estímulo. Como se ha adelantó en la introducción, diversos autores hipotetizan que la inhibición selectiva conllevaría la activación de una red de áreas corticales y subcorticales que podrían diferir (al menos en parte) de la observada en la inhibición no selectiva (simple o global) (p.e., Aron, 2011). Por ello, se requieren estudios con otras medidas de actividad cerebral que permitan explorar la conectividad entre regiones corticales y subcorticales para una mejor caracterización de la inhibición selectiva.

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